

## CLINICAL PRACTICE

# Glycaemic control in the perioperative period

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### Editor's key points

- Diabetes mellitus and other disorders of blood glucose regulation are common in perioperative patients.
- The optimal management of perioperative dysglycaemia has been shown to improve perioperative outcomes.
- Guidelines and recommendations aid in the diagnosis and management of perioperative abnormalities in glucose homeostasis.

**Summary.** The prevalence of type 2 diabetes mellitus and the potential for perioperative dysglycaemia (hyperglycaemia, hypoglycaemia, stress-induced hyperglycaemia, or glucose variability) continue to increase dramatically. The majority of investigations on perioperative glycaemic control focused on critically ill patients and concentrated on goals of therapy, level of intensity of insulin infusion, feeding regimes, concerns over hypoglycaemia, and promulgation of recent guidelines calling for less strict glucose control. Areas of perioperative glycaemic control that deserve further investigation include preoperative identification of patients with undiagnosed type 2 diabetes and other forms of dysglycaemia, determination of appropriate intraoperative glucose goals, and establishment of the impact and natural history of perioperative abnormalities in glucose homeostasis. In the heterogeneous adult perioperative population, it is unlikely that one standard of perioperative glycaemic control is appropriate for all patients. This review presents recent evidence and expert guidance to aid preoperative assessment, intraoperative management, and postoperative care of the dysglycaemic adult patient.

**Keywords:** blood, glucose; diabetes; intensive care; surgery, postoperative; surgery, preoperative

The prevalence of type 2 diabetes mellitus (DM) and perioperative dysglycaemia [hyperglycaemia, hypoglycaemia, stress-induced hyperglycaemia (SIH), or glucose variability (GV)] continue to increase dramatically. The most recent US Centers for Disease Control and Prevention National Health and Nutrition Examination Survey reports that the incidence of DM has tripled over the past decade and projections are that it may triple again within the next several decades. DM affects an estimated 25.8 million Americans (8.3% of the US population). The vast majority of these individuals (>90–95%) have type 2 DM, but roughly one-third of them remain undiagnosed ([http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf); <http://www.cdc.gov/media/pressrel/2010/r101022.html>). The World Health Organization (WHO) estimates the prevalence of DM at 60 million Europeans (10.3% of men and 9.3% of women over the age of 25) (<http://euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/diabetes/data-and-statistics>).

The majority of investigations on perioperative glycaemic control have focused on postoperative and intensive care unit (ICU) patients. This work has concentrated on goals of therapy, level of intensity of insulin infusion, feeding regimes, concerns over hypoglycaemia, and promulgation of recent guidelines calling for less strict glucose control. Areas germane to perioperative glycaemic control that deserve

further investigation include: preoperative identification of patients with undiagnosed type 2 DM and other forms of dysglycaemia, determination of appropriate intraoperative glucose goals, and establishment of the impact and natural history of perioperative abnormalities in glucose homeostasis.

The optimal management of the patient with perioperative dysglycaemia continues to be debated. Hyperglycaemia, hypoglycaemia, and GV are common features in critically ill patients.<sup>1–5</sup> Furthermore, SIH entails higher risks and often poorer outcomes in hospitalized patients when compared with equally dysglycaemic patients with known DM-induced hyperglycaemia.<sup>4–5</sup> Routine application of tight glycaemic control, however, was called into question after the results of various single-centre, 'real-world' studies and the multi-centre, multinational NICE-SUGAR trial all reported either no benefit with normalization of glucose during critical illness or an increased incidence of hypoglycaemia and mortality. Whether there is a true cause and effect association between hypoglycaemia and outcome in the critically ill remains unknown.<sup>6–7</sup>

Hospitals and institutions are encouraged to create their own policies, including in-house guidelines for DM management, which cover the spectrum of all treated patient groups, ambulatory to critically ill.<sup>3</sup> The creation of an institution-specific

multidisciplinary team consisting of nursing, case managers, and physician representatives to enhance unit or ward acceptance is suggested. The WHO surgical safety checklist bundle should be established with a target blood glucose (BG) of 6–10 mM (108–180 mg dl<sup>-1</sup>) (acceptable range 4–12 mM, 72–216 mg dl<sup>-1</sup>).<sup>8</sup>

Perioperative dysregulation of glucose homeostasis can result in elevated, lowered, or highly variable glucose levels. Pancreatic  $\beta$  cell deficiency or dysfunction, peripheral insulin resistance, inhibition of insulin release, counter-regulatory hormone modulation, or even glucose transporter deficiencies can cause these physiological perturbations. Extensive discussions about the pathophysiology of glucose regulation and DM and also management of dysglycaemia in specific perioperative patient populations (i.e. peripartum, cardiac, neurosurgical) are beyond the scope of this article and are well reviewed elsewhere.<sup>9–14</sup>

This review focuses on preoperative identification, assessment, and preparation of patients with known or previously unrecognized abnormalities in glucose homeostasis; intraoperative management of glucose abnormalities; and ward, intermediate care unit (IMCU), and ICU goals for postoperative and post-hospital discharge glucose management.

## Preoperative

Preoperative identification of patients with DM, or those at risk for perioperative dysglycaemia, provides a potential opportunity to reduce morbidity and mortality. Early identification facilitates timely intervention and allows arrangement of appropriate perioperative and long-term follow-up. Anaesthesiologists, as leaders of the 'surgical home' model, are perfectly poised to assist in this process.<sup>15</sup> Anaesthesia care providers should embrace the opportunity to assess, diagnose, and ultimately refer patients for continued care. Patient education, initiation of lifestyle changes, and implementation of therapy have been shown to favourably impact microvascular and macrovascular disease.<sup>16</sup> Despite this, no current guidelines recommend preoperative DM screening in patients without a documented history of hyperglycaemia.<sup>17</sup>

## Diagnosis

Patients with DM have increased perioperative morbidity and mortality.<sup>3, 18–23</sup> One must remember, however, that DM is often found in combination with other significant risk factors (sedentary lifestyle, smoking, obesity). These risk factors can cloud the understanding of the specific role DM plays in perioperative morbidity and mortality. Nonetheless, diabetic patients are at increased risk for postoperative infection, arrhythmia, acute renal failure, ileus,<sup>12</sup> stroke, myocardial ischaemia, increased length of hospital stay, and death.<sup>24, 25</sup> Many of these risks are present in prediabetic patients as well.<sup>26, 27</sup> The American Diabetes Association (ADA) suggests screening for DM in all adults at age 45 yr and earlier in those with a BMI  $\geq 25$  kg m<sup>-2</sup> and one or more identified risk factors (Table 1),<sup>28</sup> and recommends placing individuals into one of three categories: normal, increased risk (prediabetic),

**Table 1** Criteria for testing for DM in asymptomatic adult individuals. \*At-risk BMI may be lower in some ethnic groups; HDL, high density lipoprotein; HA<sub>1</sub>C, haemoglobin A<sub>1</sub>C; IGT, impaired glucose tolerance; IFG, impaired fasting glucose. Modified and reprinted with permission from the American Diabetes Association<sup>29</sup>

- (1) Testing should be considered in all adults who are overweight (BMI  $\geq 25$  kg m<sup>-2</sup>) and have additional risk factors:
  - Physical inactivity
  - First-degree relative with diabetes mellitus
  - High-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander)
  - Women who delivered a baby weighing  $>4.08$  kg or were diagnosed with gestational diabetes mellitus
  - Hypertension ( $\geq 140/90$  mm Hg or on therapy for hypertension)
  - HDL cholesterol level  $<0.90$  mM (35 mg dl<sup>-1</sup>), a triglyceride level  $>2.8$  mM (250 mg dl<sup>-1</sup>), or both
  - Women with polycystic ovary syndrome
  - HA<sub>1</sub>C  $\geq 5.7\%$ , IGT, or IFG on previous testing
  - Other clinical condition associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)
  - History of cardiovascular disease
- (2) In the absence of above criteria, testing for diabetes mellitus should begin at age 45 yr
- (3) If results are normal, testing should be repeated at least at 3 yr intervals, with consideration of more frequent testing depending upon the initial results (e.g. those with prediabetes should be tested yearly) and risk status

**Table 2** Categories of increased risk for DM (prediabetes). For all three tests, the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range. FPG, fasting plasma glucose; 2-H OGTT, 2 h oral glucose tolerance test; HA<sub>1</sub>C, haemoglobin A<sub>1</sub>C. Normal individuals are defined as having an FPG  $\leq 5.5$  mM (100 mg dl<sup>-1</sup>) (no caloric intake for  $>8$  h). Modified and reprinted with permission from the American Diabetes Association<sup>29</sup>

1. FPG 5.6–6.9 mM (100–125 mg dl<sup>-1</sup>) or,
2. 2-H OGTT 7.0–11.0 mM (140–199 mg dl<sup>-1</sup>) or,
3. HA<sub>1</sub>C 5.7–6.4%

and diabetic based upon fasting plasma glucose (FPG), haemoglobin A<sub>1</sub>C (HA<sub>1</sub>C), and 2 h oral glucose tolerance test (2-H OGTT) results (Tables 2 and 3).<sup>29</sup> These guidelines are broader than the US Preventive Health Taskforce recommendations,<sup>30</sup> which are undergoing revision and have been shown to underestimate significantly the prevalence of hyperglycaemia (<http://uspreventiveservicestaskforce.org/uspsttopics.htm>).

## Undiagnosed DM

Not all patients with DM are aware of their status. A 2010 Cleveland Clinic study found the rate of undiagnosed DM in 39 434 non-cardiac surgery patients was 10% and impaired fasting glucose (IFG) 11%.<sup>31</sup> Sheehy and colleagues<sup>15</sup> showed that 24% of insured, elective surgery patients with recent primary care visits had either undiagnosed DM or IFG discovered the

**Table 3** Criteria for the diagnosis of DM. HA<sub>1</sub>C, haemoglobin A<sub>1</sub>C; FPG, fasting plasma glucose; 2-H OGTT, 2 h oral glucose tolerance test. Modified and reprinted with permission from the American Diabetes Association<sup>29</sup>

1. HA<sub>1</sub>C  $\geq 6.5\%$  or,
2. FPG  $\geq 7.0$  mM (126 mg dl<sup>-1</sup>) or,
3. 2-H OGTT  $\geq 11.1$  mM (200 mg dl<sup>-1</sup>) or,
4. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose  $\geq 11.1$  mM (200 mg dl<sup>-1</sup>)

day of surgery. Lauruschkat and colleagues<sup>32</sup> found the incidence of undiagnosed DM in 7310 German patients undergoing coronary artery bypass grafting (CABG) to be 5.2% (known DM 29.6%). Interestingly, patients with undiagnosed DM were more likely to require resuscitation, re-intubation, and longer postoperative ventilation, and had higher perioperative mortality than both those without DM and those with known DM.<sup>32</sup> This finding, along with those of other investigators, suggests that undiagnosed DM is an even greater risk factor for perioperative morbidity and mortality than known DM.<sup>33</sup> This increased risk may be related to various factors, including poor preventive care and less aggressive therapy by the hospital-based team.

### The role of HA<sub>1</sub>C

HA<sub>1</sub>C provides insight into glucose control over the preceding 3–4 months. Elevated preoperative HA<sub>1</sub>C is associated with increased perioperative risk and holds promise as a preoperative screening modality.<sup>34–35</sup> Gustafsson and colleagues,<sup>35</sup> in a prospective study of 120 patients without known DM having major colorectal surgery, were able to show patients with preoperative HA<sub>1</sub>C > 6% were at significantly greater risk for pneumonia, urinary tract infection, pleural effusions, and postoperative ileus, and had significantly elevated postoperative glucose levels in this group of patients. Others retrospectively linked preoperative HA<sub>1</sub>C to postoperative complications. Dronge and colleagues<sup>36</sup> showed that preoperative HA<sub>1</sub>C < 7% is significantly associated with decreased infectious complications including pneumonia, wound infection, urinary tract infection, and sepsis. Hudson and colleagues<sup>37</sup> demonstrated a preoperative HA<sub>1</sub>C > 6% in non-diabetics is independently associated with greater early mortality after elective cardiac surgery.

Elevated HA<sub>1</sub>C, as a marker of poor glycaemic control, correlates with increased perioperative risk in diabetic patients. Han and Kang<sup>38</sup> demonstrated a significant increase in wound complications after total knee arthroplasty in diabetic patients with HA<sub>1</sub>C > 8%. Diabetic patients with an HA<sub>1</sub>C > 6.5% have an increased risk of pneumonia, urinary tract infection, and superficial wound infections after elective cardiac surgery when compared with diabetics with HA<sub>1</sub>C < 6.5%.<sup>34</sup> Currently, the ADA suggests that practitioners consider obtaining an HA<sub>1</sub>C on diabetic patients admitted to the hospital if the result of testing in the previous 2–3 months is not available.

The ADA also suggests HA<sub>1</sub>C testing in patients with risk factors for undiagnosed DM who exhibit hyperglycaemia in the hospital.<sup>29</sup>

Although elevated HA<sub>1</sub>C is associated with adverse outcomes, there is a lack of data to show delaying elective surgery to correct HA<sub>1</sub>C is beneficial. Nonetheless, HA<sub>1</sub>C screening does allow identification of unrecognized DM and stratification of perioperative risk. Aggressive approaches to lowering HA<sub>1</sub>C in non-surgical patients have not been shown to decrease mortality.<sup>39</sup> Future investigations will likely clarify the role of preoperative HA<sub>1</sub>C management on modifying surgical outcome.

Clinicians should be reminded that the accuracy of HA<sub>1</sub>C can vary by measurement technique. Erroneous results are possible in patients with haemoglobinopathies, chronic bleeding, iron deficiency, renal failure-induced anaemia, recent transfusions, or ongoing haemolysis.<sup>40</sup>

### Hyperglycaemia

Preoperative hyperglycaemia, independent of diabetic status, increases the risk of perioperative morbidity and mortality.<sup>9</sup> In a retrospective review of patients who developed periprosthetic joint infection after elective primary total hip or total knee arthroplasty, preoperative BG was significantly elevated compared with control patients.<sup>41</sup> Preoperative BG > 11.1 mM (200 mg dl<sup>-1</sup>) is associated with deep sternal wound infections in patients undergoing CABG,<sup>42</sup> and preadmission hyperglycaemia is an independent risk factor for in-hospital symptomatic pulmonary embolism after major orthopaedic surgery.<sup>43</sup> Hyperglycaemia before carotid endarterectomy is associated with increased risk of perioperative stroke, transient ischaemic attack, myocardial infarction, and death.<sup>44</sup>

The incidence of preoperative hyperglycaemia is striking. In a prospective study of 493 non-diabetic patients undergoing elective, non-cardiac surgery, 25% of patients had elevated FPG the morning of surgery.<sup>45</sup> Interestingly, known diabetic status has been shown to provide some protection from the adverse effects of hyperglycaemia.<sup>5–46–47</sup> For patients on general hospital wards without a history of DM, admission hyperglycaemia increases mortality, length of stay (LOS), and likelihood of discharge to a transitional care unit when compared with known diabetics.<sup>5</sup> Whether this increase in morbidity and mortality is related to undertreatment of elevated glucose or other variables remains unknown.

Preoperative hyperglycaemia might not be related to DM, but instead may be a response to acute illness or injury. This 'SIH' is defined as elevated BG that reverts to normal after illness subsides and counter-regulatory hormone and inflammatory mediator surge abates.<sup>48–49</sup> While physiologic, SIH appears to independently increase the risk of perioperative and critical illness morbidity and mortality.<sup>48–50–52</sup> Kerby and colleagues<sup>52</sup> evaluated 6852 consecutive trauma patients for the presence of SIH. These patients had an admission glucose of  $\geq 11.1$  mM (200 mg dl<sup>-1</sup>), HA<sub>1</sub>C < 6.5% (not diabetic by HA<sub>1</sub>C criteria), and no past medical history of DM. When matched with a control group of similar age, sex, injury severity

score, and revised trauma score, the SIH patients had a more than two-fold increase in mortality. Surprisingly, admission hyperglycaemia in diabetic patients did not significantly increase mortality.<sup>52</sup> In a retrospective study of 110 consecutive orthopaedic trauma patients, Karunakar and Staples<sup>53</sup> found that a mean perioperative BG  $>12.2$  mM ( $220$  mg dl<sup>-1</sup>) was associated with seven-fold higher risk of infection in patients with no known history of DM compared with matched diabetic patients. These data suggest that SIH can be a marker for severity of illness and degree of counter-regulatory hormone surge. One could also infer that previously diagnosed DM is in some way protective, as opposed to new-onset SIH (with no history of DM), although further investigations designed to answer this question are needed.

### Glucose variability

GV, defined as the degree of glucose level excursion over time, is increasingly linked to poor ICU and perioperative outcomes. In 2006, Egi and colleagues<sup>54</sup> retrospectively looked at both the mean glucose and standard deviation (SD) of BG, as a marker of GV, in 7049 ICU patients. The authors found that both the mean and SD of BG were significantly associated with ICU mortality.<sup>54</sup> Subsequently, in 2008, Krinsley showed that the SD of BG level was a predictor of mortality even within different ranges of mean glucose. They also demonstrated GV to be a stronger predictor of mortality than mean glucose.<sup>55</sup> Further defining the effects of GV in an ICU population, Hermanides and colleagues<sup>56</sup> were able to show that the combination of high GV and high mean glucose values was associated with the highest overall ICU mortality. Interestingly, low GV was protective even in patients with high mean glucose levels. Their findings suggest that high mean glucose is less harmful when GV is low, and patients with identical mean glucose can have different mortality rates depending on their GV.<sup>56</sup> A clear cause-and-effect relationship, rather than just a simple association between GV and morbidity and mortality, has not been clearly established. Further investigations are needed to better delineate the importance of GV in the perioperative period.

### Preoperative evaluation and management

Patients at risk for perioperative dysglycaemia, whether they are diabetic, prediabetic, or have SIH, deserve special consideration before operation. Currently, there are limited data to suggest that significant preoperative interventions aimed at controlling dysglycaemia have an impact on outcome. The aforementioned evidence seems to infer, however, that early identification of these patients, if doing nothing more than identifying them as 'at risk' and subsequently increasing provider vigilance, could have a significant impact on outcome. Anaesthesia providers are perfectly poised to initiate this process. Future investigations will further delineate the role of early identification and any potential benefits of early treatment.

Patients with a known history of DM should be thoroughly evaluated before entering the operating suite. One should

have a detailed understanding of the history of the patient's disease, including: specific diagnosis (type 1 DM, type 2 DM, gestational diabetes, etc.), duration of illness, current treatment modalities, adequacy of control, and the presence and severity of co-morbidities. This discussion will focus on patients with a diagnosis of type 2 DM. It should be remembered, however, that type 1 DM patients have an obligate physiological need for exogenous insulin (as they are unable to produce their own), have normal insulin sensitivity, and can have significant comorbidities.<sup>57</sup>

Tables 4–6 provide a brief overview of the pharmacology of common oral antidiabetic agents, non-insulin injectables, and insulins. The preoperative management of diabetic medications should be tailored to the individual patient. Most authors suggest holding oral antidiabetic agents and non-insulin injectable medications on the day of surgery and not before.<sup>58</sup> At least one set of guidelines suggests holding metformin for 24–48 h before operation in patients with renal dysfunction and in those who might receive i.v. contrast to decrease the risk of perioperative lactic acidosis.<sup>58</sup> Management of preoperative insulin therapy should focus on the avoidance of hypoglycaemia while maintaining reasonable BG control. Patients at risk for hypoglycaemia before operation include those with very strict glycaemic control, those with significant daily GV, those with complicated insulin regimens, and those who are taking insulin in combination with oral antidiabetic agents.<sup>59 60</sup> The majority of patients who receive insulin are using a basal/bolus insulin schedule.<sup>29 61</sup> Long-acting agents are intended to supply a steady, basal supply of insulin while shorter-acting agents (often referred to as bolus, correctional or nutritional insulin) are used to counter acute (post-prandial) increases in BG. Table 7 outlines a general approach to the preoperative management of insulin. This approach recommends modest alteration in long-acting insulin and elimination of short-acting insulin on the day of surgery.<sup>58</sup>

Preoperative laboratory investigations in known diabetics should include HA<sub>1</sub>C if not drawn in the previous 2–3 months,<sup>29</sup> preoperative BG, and any additional testing needed to further delineate the existence or severity of common comorbidities (i.e. nephropathy, cardiomyopathy). The ADA recommends outpatient DM management to achieve an HA<sub>1</sub>C  $< 7\%$  (normal 4–7%).<sup>29</sup> Although current guidelines do not support liberal preoperative HA<sub>1</sub>C or BG screening, it may be wise to expand such screening in certain patient populations (i.e. cardiac, neurological, orthopaedic, transplant, and trauma surgery).<sup>62</sup> This would aid providers in identifying patients with previously undiagnosed dysglycaemia, clarify glucose control over the previous 3 months, and potentially increase provider vigilance during the perioperative period.

## Intraoperative

### Hyperglycaemia

There are little data looking specifically at intraoperative BG management and its effects on postoperative outcomes. Existing data are heavily skewed towards the cardiac surgical



**Table 4** Pharmacology of oral antidiabetic agents. Modified with permission from SAMBA<sup>58</sup>

Drug class: generic (trade name)	Mechanism of action	Half-life (h)	Adverse effects
Biguanides	Decrease hepatic gluconeogenesis, increase insulin sensitivity	6–18	Diarrhoea, nausea, vomiting, lactic acidosis
Metformin (Glucophage)		24	
Metformin extended release			
Sulphonylureas	Stimulate insulin secretion, decrease insulin resistance	2–10	Hypoglycaemia, lactic acidosis
Chlorpropamide (Diabinese)			
Tolbutamide (Orinase)			
Glimepiride (Amaryl)			
Glipizide (Glucotrol)			
Glyburide (Diabeta, Micronase)			
Meglitinides	Stimulate pancreatic insulin secretion	1	Hypoglycaemia
Repaglinide (Prandin)			
Nateglinide (Starlix)			
Thiazolidindiones	Regulate carbohydrate and lipid metabolism, reduce insulin resistance and hepatic glucose production	3–8	Fluid retention, increased cardiac risk including congestive heart failure, hepatotoxicity
Rosiglitazone (Avandia)			
Pioglitazone (Actos)			
$\alpha$ -Glucosidase inhibitors	Reduce the intestinal absorption of ingested glucose	2–4	Gastrointestinal irritation, flatulence
Acarbose (Precose)			
Miglitol (Glyset)			
Dipeptidyl peptidase-4 (DDP-4) inhibitors	Reduces breakdown of hormone-incretins (glucagon-like peptide type-1), enhance insulin secretion, decrease glucagon		
Sitagliptin (Januvia)			
Saxagliptin (Onglyza)			

**Table 5** Non-insulin injectables. Modified with permission from SAMBA<sup>58</sup>

Drug class: generic (trade name)	Mechanism of action	Half-life (h)	Adverse effects
Exenatide (Byetta)	Synthetic form of exendin 4, which has actions similar to glucagon-like peptide type-1 Suppresses glucagon secretion and hepatic glucose production Suppresses appetite Delays gastric emptying	6–10	Nausea, vomiting, weight loss, hypoglycaemia when combined with sulphonylureas
Exenatide extended-release (Bydureon)	Weekly dosing, see exenatide	Days	Medullary thyroid cancer, acute pancreatitis
Pramlintide (Symlin)	Synthetic form of amylin, a naturally occurring peptide that is cosecreted with insulin by $\beta$ cells Suppresses post-prandial glucagon secretion and hepatic glucose production Enhances the effects of insulin Suppresses appetite Delays gastric emptying	2–4	Nausea, vomiting, weight loss, hypoglycaemia with insulin
Liraglutide (Victoza)	Long-acting glucagon-like peptide type-1 agonist	11–15	Medullary thyroid cancer

**Table 6** Pharmacology of insulin. Modified with permission from SAMBA<sup>58</sup>

Drug class: generic (trade name)	Onset	Peak effect	Duration
Short acting and rapid acting			
Regular (Novolin R, Humulin R)	30–60 min	2–4 h	6–8 h
Lispro (Humalog)	5–15 min	30–90 min	4–6 h
Aspart (Novolog)	5–15 min	30–90 min	4–6 h
Glulisine (Apidra)	5–15 min	30–90 min	4–6 h
Intermediate acting			
NPH (Novolin N, Humulin N-NF)	2–4 h	4–10 h	10–16 h
Zinc insulin (Lente)	2–4 h	4–10 h	12–20 h
Extended zinc insulin (Ultralente)	6–10 h	10–16 h	18–24 h
Long acting (peakless)			
Glargine (Lantus)	2–4 h	None	20–24 h
Detemir (Levemir)	2–4 h	None	20–24 h
Mixed insulins (NPH+regular)			
70% NPH/30% regular (Novolin 70/30, Humulin 70/30)	30–90 min	Dual	10–16 h
50% NPH/50% regular (Humulin 50/50)	30–90 min	Dual	10–16 h
Mixed insulins (intermediate-acting+rapid-acting analogues)			
70% Aspart Protamine suspension/30% Aspart (Novolog mix 70/30)	5–15 min	Dual	10–16 h
75% Lispro Protamine suspension/25% Lispro (Humalog mix 75/25)	5–15 min	Dual	10–16 h
50% Lispro Protamine suspension/50% Lispro (Humalog mix 50/50)	5–15 min	Dual	10–12 h

population.<sup>63–66</sup> In 2007, Gandhi and colleagues<sup>67</sup> reported a retrospective investigation of 409 consecutive patients undergoing cardiac surgery at the Mayo Clinic. Patients who experienced one of the primary endpoints (death, infectious, cardiac, neurological, renal, or pulmonary) had significantly higher initial, mean, and maximal intraoperative BG values. Logistic regression analysis indicated that a 1.1 mM (20 mg dl<sup>-1</sup>) increase in the mean intraoperative BG concentration >5.5 mM (100 mg dl<sup>-1</sup>) was associated with a 34% increase in experiencing a primary endpoint.<sup>67</sup> Doenst and colleagues,<sup>65</sup> in another cardiac surgical population, showed high peak BG ≥20 mM (360 mg dl<sup>-1</sup>) was an independent predictor of morbidity and mortality in diabetic and non-diabetic patients. Interestingly, patients with BG levels <15 mM (270 mg dl<sup>-1</sup>) were not subject to worse outcomes.<sup>65</sup> Ouattara and colleagues<sup>66</sup> reported intraoperative hyperglycaemia, defined as more than four consecutive BG values >11.1 mM (200 mg dl<sup>-1</sup>) in a study of 200 diabetic patients undergoing cardiac surgery, was associated with poor cardiac and non-cardiac outcomes.

### Intensive insulin therapy or conventional therapy

Historically, providers often allowed 'permissive hyperglycaemia' under the (mis)assumption that the body needed fuel to overcome surgical stress or critical illness.<sup>68–69</sup> This approach was called into question after the landmark ICU investigation by Van den Berghe and colleagues in 2001.<sup>70</sup> This single-centre (Leuven, Belgium), randomized control trial of 1548 mechanically ventilated, surgical ICU patients compared intensive insulin therapy (IIT) with conventional treatment. The BG target in the IIT group was 4.4–6.1 mM (80–110 mg dl<sup>-1</sup>), and 10–11.1 mM (180–200 mg dl<sup>-1</sup>) in the control group. The IIT group had reduced overall in-hospital mortality, bloodstream infections, acute renal failure requiring dialysis or haemofiltration, median number of red cell transfusions, and critical illness polyneuropathy, and also shorter length of mechanical ventilation and ICU stay. Mortality benefit was

**Table 7** Instructions regarding preoperative insulin. Modified with permission from SAMBA<sup>58</sup>

Insulin regimen	Day before surgery	Day of surgery	Comments
Insulin pump	No change	No change	Use 'sick day' or sleep basal rates for outpatient surgery, discontinue if planned admission
Long acting, peakless insulins	No change	75–100% of morning dose	Reduce nighttime dose if history of nocturnal or morning hypoglycaemia On the day of surgery, the morning dose of basal insulin may be administered on arrival to facility See comments for long-acting insulins
Intermediate-acting insulins	No change in daytime dose, 75% of dose if taken in the evening	50–75% of morning dose	
Fixed combination Insulins	No change	50–75% of morning dose of intermediate-acting component	Lispro-protamine only available in combination; therefore, use NPH instead on day of surgery See comments for long-acting insulins
Short- and rapid-acting insulins	No change	Hold the dose	
Non-insulin injectables	No change	Hold the dose	

greatest in patients with an ICU stay  $\geq 5$  days. Patients in the IIT arm, however, had significantly more hypoglycaemic events ( $BG \leq 2.2$  mM or  $40$  mg  $dl^{-1}$ ) (5.1% vs 0.8%) with no association between hypoglycaemia and death.<sup>70</sup> Various study limitations were present, including the single-centre approach, unblinded design, lack of targeted intraoperative glucose control, and inclusion of primarily post-cardiac surgery patients (63%) who received an atypical feeding protocol. An unusually high mortality rate was also present in the control group.<sup>71</sup> Despite these limitations, this study is often referred to as 'that which launched a thousand protocols'.<sup>72</sup>

A second Leuven study published in 2006 compared IIT with conventional therapy in 1200 medical ICU patients. It demonstrated a decrease in renal injury, days of mechanical ventilation, ICU LOS, and hospital LOS. It did not, however, show any mortality benefit with IIT. Hypoglycaemic events were more prevalent in the IIT group (18.7% vs 3.1%), likely related in part to glucose measurement methodology. Importantly, multivariate analysis demonstrated hypoglycaemia to be an independent predictor of death.<sup>73</sup> Pooled analysis of the two Leuven studies suggested maintaining BG levels  $<8.3$  mM ( $150$  mg  $dl^{-1}$ ) to be the most important factor in reducing mortality. In order to achieve renal and nervous system protection, BG had to be kept  $<6.1$  mM ( $110$  mg  $dl^{-1}$ ). This tight level of control did provide additional survival benefit. The pooled data reaffirm the higher risk of hypoglycaemic events in the IIT group (11.3% vs 1.8%).<sup>74</sup>

The risks of IIT were highlighted with the publication of another landmark study, Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR). The goal of this study was to compare IIT (BG goal 4.5–6 mM, 81–108 mg  $dl^{-1}$ ) with conventional treatment (BG goal 8–10 mM, 144–180 mg  $dl^{-1}$ ). The NICE-SUGAR trial was multicentre, international, and randomized. It included 6104 mixed medical and surgical (35%) ICU patients. The authors were not able to demonstrate a difference in hospital or ICU LOS, length of mechanical ventilation, or the need for renal replacement. In contrast to the initial Leuven study, mortality rates were higher in the IIT group (27.5% vs 24.9%). The NICE-SUGAR trial reaffirmed a higher incidence of hypoglycaemia in the IIT group. Along with other studies of its era, NICE-SUGAR questioned the safety of IIT in critically ill patients.<sup>75–77</sup>

Is there a role for intraoperative IIT? A study published in 2007 by Gandhi and colleagues<sup>64</sup> attempted to answer this question in a randomized, prospective fashion. Four hundred adult patients undergoing elective cardiac surgery were randomized to either an IIT group (BG goal 4.4–5.5 mM, 80–100 mg  $dl^{-1}$ ) or a conventional treatment group (patients not given insulin until BG  $>11.1$  mM, 200 mg  $dl^{-1}$ ). Both groups were treated with insulin infusion after surgery to maintain normoglycaemia. The authors found more deaths (4 vs 0,  $P=0.061$ ) and significantly more strokes (8 vs 1,  $P=0.02$ ) in the IIT group. This finding led investigators to question the safety of intraoperative IIT.<sup>64</sup> A 2012 meta-analysis by Hua and colleagues,<sup>78</sup> however, were able to show some benefit of intraoperative IIT. Data were pooled from five randomized control

trials; a total of 706 adult cardiac surgical patients were assigned to either IIT or conventional therapy. There was no statistically significant difference in 30 day or in-hospital mortality (although the IIT group had seven deaths, and the conventional treatment group had three). There was also no difference in the number of hypoglycaemic events. Infection rates, however, were significantly lower in the IIT group. The authors caution that larger randomized trials are required before the implementation of any strong, evidence-based recommendations regarding intraoperative IIT.<sup>78</sup>

## Treatment goals

Intraoperative IIT is currently not recommended because of conflicting data and the risk of hypoglycaemia. The Society for Ambulatory Anesthesia (SAMBA) and several authors suggest following guidelines published by the American Association of Clinical Endocrinologists (AACE) and the ADA in their Consensus Statement on Inpatient Glycemic Control.<sup>58 79</sup> This group suggests initiating treatment with an insulin infusion in critically ill patients at a BG no greater than 10 mM ( $180$  mg  $dl^{-1}$ ). Once treatment has begun, they suggest a target BG of 7.7–10 mM ( $140$ – $180$  mg  $dl^{-1}$ ), recognizing that greater benefit might be realized at the lower end of this range. Finally, they admit that even lower targets might be beneficial in some patient populations, but suggest never setting a BG target below 6.1 mM ( $110$  mg  $dl^{-1}$ ).<sup>79</sup> There are slight variations in suggested treatment thresholds and target glucose levels when looking at recommendations from other prominent medical societies; most, however, mirror those of the ADA.<sup>20 80 81</sup>

## Measurement and monitoring

Although the ADA recommends the use of insulin infusions for critically ill patients, both the ADA and SAMBA suggest the use of subcutaneous insulin for non-critical patients.<sup>29 58</sup> This is less labour intensive and more practical than i.v. administration in an outpatient setting.<sup>82</sup> Absorption of subcutaneously administered insulin can be variable, the time to onset can be prolonged, and repeated doses can become 'stacked', increasing the risk of hypoglycaemia.<sup>58 68</sup> I.V. insulin has the advantage of being quickly titratable with a rapid onset of action. Insulin, irrespective of the route of administration, is a dangerous drug; it is one of the five most common drugs involved in clinically significant medical errors, and has the highest rate of administration errors.<sup>10 83</sup>

The recommended frequency of intraoperative BG monitoring depends on many factors. In metabolically stable diabetic patients undergoing short ( $<2$  h), outpatient procedures, it is only necessary to check BG on admission, before operation, and on discharge. For longer outpatient procedures or for patients receiving intraoperative subcutaneous insulin, it is advisable to check BG levels every 1–2 h.<sup>58</sup> Finally, for higher acuity patients, patients having extensive surgical procedures, or patients on insulin infusions, the ADA recommends BG monitoring as frequently as every 30 min.<sup>29</sup>

Point-of-care (POC) testing is appropriate for BG measurement in metabolically stable patients. This testing technique, however, is considered less accurate than central laboratory testing.<sup>84</sup> The National Committee for Clinical Laboratory Standards recommends differences between POC testing and central laboratory testing not exceed  $\pm 15\%$  when glucose concentrations are  $<5.5$  mM ( $100$  mg  $\text{dl}^{-1}$ ) and  $\pm 20\%$  when glucose concentrations are  $>5.5$  mM ( $100$  mg  $\text{dl}^{-1}$ ).<sup>85</sup> Most authors suggest a relatively high hypoglycaemia alert value (e.g.  $3.9$  mM,  $70$  mg  $\text{dl}^{-1}$ ) when using POC testing devices and more frequent monitoring and routine central laboratory confirmation of abnormal values.<sup>58</sup> Many factors increase the disparity between POC and central laboratory glucose measurements. These include haemodynamic instability, shock, anaemia, elevated bilirubin, uric acid, severe hyperlipidaemia, and various medications including L-dopa, dopamine, mannitol, acetaminophen, and maltose.<sup>9 10 84</sup> Most experts recommend central laboratory testing or arterial blood gas analysis for measurement of glucose in haemodynamically or metabolically unstable patients.<sup>9 10 58 84</sup>

## Postoperative care

The following reviews guidelines, recommendations, and results of clinical trials aimed at compiling statements and suggestions for postoperative glucose control covering a spectrum of patients from those being discharged after ambulatory surgery to those who require intensive care.

### Post-anaesthesia care unit

The Diabetes UK Position Statements and Care Recommendations suggest maintaining BG in the range of  $6$ – $10$  mM ( $108$ – $180$  mg  $\text{dl}^{-1}$ ) if safely achievable.<sup>3</sup> Otherwise, a wider target range of  $4$ – $12$  mM ( $72$ – $216$  mg  $\text{dl}^{-1}$ ) is acceptable.<sup>3</sup> The correction of high BG can be achieved using subcutaneous insulin or i.v. insulin.<sup>3</sup> Depending on the present state and comorbidities of an individual patient, capillary, venous, or arterial BG levels must be assessed at least hourly, or more frequently if readings are outside the target range.<sup>3</sup>

Aggressive nausea and vomiting prophylaxis and avoidance of factors that might increase postoperative nausea and vomiting (PONV), such as administration of opioids, should allow early resumption of oral intake. Dexamethasone, a well-established antiemetic, is frequently used for prevention of

PONV.<sup>86</sup> Its use, even in small doses, has been shown to transiently increase BG levels. Dysglycaemic patients receiving dexamethasone, or other steroid medications, should have appropriate monitoring of BG levels and correction of hyperglycaemia as needed.<sup>58</sup>

### Ambulatory patients: SAMBA guidelines

Thanks to a comprehensive consensus statement issued by SAMBA, we now have definitive guidelines to address the management of diabetic patients undergoing ambulatory surgery procedures.<sup>58</sup> Outpatient postoperative patients with abnormal glucose homeostasis should be observed in an ambulatory facility until the possibility of hypoglycaemia from perioperatively administered insulin is excluded and discharge criteria are met (Table 8).<sup>87</sup> Most ambulatory patients are able to start early oral intake to counteract potential hypoglycaemia. If this is not the case, they should be monitored for an appropriate period of time after the last dose of insulin. The potential of subcutaneous rapid-acting nutritional insulin to provoke hypoglycaemia abates within  $1.5$  h (Table 6) in contrast to subcutaneous regular insulin, which subsides  $3$ – $4$  h after the last dose is administered.<sup>59 61</sup> More frequent measurements than every hour may be indicated for patients receiving intraoperative insulin and in the case of lower BG levels.<sup>58</sup>

### Intensive care unit

#### Glycaemic control in critically ill patients: waiting for definitive answers

Critically ill patients frequently develop hyperglycaemia, even without previous evidence of DM.<sup>1</sup> Before 2001, SIH in critically ill patients was generally accepted as physiologic.<sup>70</sup> In the aftermath of the Leuven trials, the concept of tight glucose control was enthusiastically incorporated into guidelines including the Surviving Sepsis Campaign 2004<sup>88</sup> and 2008,<sup>89</sup> and those of the ADA<sup>90</sup> and the AACE.<sup>91</sup> Subsequent trials only partially supported these findings or even failed to show a difference with regard to mortality, revealing high incidences of severe hypoglycaemic events as the most harmful complication.<sup>64 73 92–101</sup>

While hyperglycaemia must be avoided, an optimal glucose range for critically ill patients is a topic of ongoing discussion. One trial reported the highest survival rates in ICU patients with glucose levels between  $6.2$  and  $8$  mM ( $111$ – $144$  mg  $\text{dl}^{-1}$ ),

**Table 8** Guidelines for glucose management in ambulatory patients<sup>58</sup>

Educate patients about signs and symptoms of potential hypoglycaemia and means to treat ( $15$ g of oral dextrose to raise BG by $2.1$ mM or $38$ mg $\text{dl}^{-1}$ over $20$ min). Best to use dextrose or sucrose tablets <sup>126</sup>
Follow routine antidiabetic (oral agents or insulin) guidelines for day of surgery
Check blood glucose on admission, before surgery, and before discharge at a minimum
Point-of-care monitoring is sufficient for stable patients; higher threshold values for hypoglycaemia (e.g. $<3.9$ mM or $70$ mg $\text{dl}^{-1}$ ) and more frequent monitoring may be indicated to ensure patient safety
Provide educational material about restarting diet, oral antidiabetic agents, and insulin after discharge
Avoid overlap between pre-, intra-, and postoperative insulin
Resumption of preoperative antidiabetic regime should be based on perioperative course and is dependent on oral intake



and the highest mortality rates with glucose levels >11.1 mM (200 mg dl<sup>-1</sup>).<sup>102</sup>

Updated guidelines have reached a compromise and generally recommend a BG target of 7.7–10 mM (140–180 mg dl<sup>-1</sup>) for inpatients as long as these levels can be safely achieved.<sup>79 80 103–105</sup>

Glucose targets and hyperglycaemia

Available studies on glucose targets in critically ill patients are difficult to interpret because of substantial differences in study populations and patient management at various centres. Table 9 covers recommended glucose targets issued by diverse societies including adaptations for subgroups at particular risk, covering cardiac surgery, trauma, and neurological patients.

The rationale of the Society of Critical Care Medicine’s practical guideline to start insulin infusion therapy at 8.3 mM

(150 mg dl<sup>-1</sup>) is rooted in their meta-analysis indicating a small, but significant, reduction in the odds ratio for hospital mortality without affecting ICU mortality.<sup>105</sup> Higher trigger values and BG excursions >10 mM (180 mg dl<sup>-1</sup>) are associated with immunosuppressive effects and the potential to exceed the renal threshold for glucosuria.<sup>105</sup> Other societies’ guidelines propose a more relaxed BG trigger value of 10 mM (180 mg dl<sup>-1</sup>) to initiate insulin infusion,<sup>29 96</sup> as there is no evidence that targets between 7.7 and 10 mM (140–180 mg dl<sup>-1</sup>) differ from the lower target values of 6.1–7.7 mM (110–140 mg dl<sup>-1</sup>).<sup>103</sup>

Hypoglycaemia: adaptation of targets and treatment

Patients with moderate (BG 2.3–3.9 mM, 41–70 mg dl<sup>-1</sup>) or severe (BG <2.2 mM, 40 mg dl<sup>-1</sup>) hypoglycaemia have been found to have a higher risk of death compared with those without hypoglycaemia.<sup>6</sup> Even one episode of hypoglycaemia

**Table 9** Recommended glucose target ranges for intensive care patients and related subgroups

Society, guideline	Patient group	Trigger BG value to start insulin infusion, mM (mg dl <sup>-1</sup> )	Target range, mM (mg dl <sup>-1</sup> )	Rationale
Society of Critical Care Medicine’s clinical practice guideline <sup>105</sup>	General recommendation	8.3 (150)	5.6–8.3 (100–150)	
	Cardiac surgery		<8.3 (150)	Decreased risk for deep sternal wound infection and death <sup>70 127–130</sup>
	Critically ill trauma patients	8.3 (150)	<10 (180)	
	Traumatic brain injury <sup>131 132</sup>	8.3 (150)	<10 (180)	
	Neurological ICU patients	8.3 (150)	<10 (180)	
	- Ischaemic stroke <sup>133–135</sup> - Intraparenchymal haemorrhage <sup>136</sup> - Aneurysmal subarachnoid haemorrhage <sup>137–139</sup>			
American Diabetes Association guidelines <sup>29</sup>	General recommendation	10 (180)	7.8–10 (140–180)	
	Adaptation		6.1–7.8 (110–140)	Adjust to lower target range in documented low rate of severe hypoglycaemia
American Association of Clinical Endocrinologists <sup>111</sup>	General recommendation		7.8–10 (140–180)	
	Surgical patients		Lower range	Only in units showing low rates of hypoglycaemia
Surviving Sepsis Campaign <sup>103</sup>	General recommendation	10 (180)	<10 (180)	Based on NICE-SUGAR study
Clinical Practical Guideline from the American College of Physicians <sup>80</sup>	General recommendation		7.8–11.1 (140–200)	If insulin infusion is applied. But guideline does not recommend intensive insulin therapy
Spanish Society of Intensive Care Medicine and Coronary Units <sup>140</sup>	General recommendation		<8.3 (150)	
French Society of Anaesthesia and Intensive Care <sup>106</sup>	General recommendation		10 (180)	
	Surgical patients		<6.1 (110)	
	Cardiac patients		<6.1 (110)	
Society of Thoracic Surgeons <sup>20</sup>	Cardiac surgery patients		<10 (180) except <8.3 (150) for those with devices in place	

is associated with higher mortality.<sup>94</sup> BG values  $<2.2$  mM ( $40$  mg  $\text{dl}^{-1}$ ) are an independent risk factor for mortality after adjustment for severity of illness, age, mechanical ventilation, renal failure, sepsis, and DM.<sup>7</sup>

French guidelines define hypoglycaemia as BG  $<3.3$  mM ( $60$  mg  $\text{dl}^{-1}$ ) and severe hypoglycaemia as BG  $<2.2$  mM ( $40$  mg  $\text{dl}^{-1}$ ).<sup>106</sup> Jacobi and colleagues<sup>105</sup> propose an adapted lower limit of  $3.9$  mM ( $70$  mg  $\text{dl}^{-1}$ ) for ICU trauma patients, with the aim of lower infection rates and shorter ICU stays.<sup>107 108</sup> For patients with brain injury, the lowest acceptable BG level is  $5.5$  mM ( $100$  mg  $\text{dl}^{-1}$ ), as hypoglycaemia increases the risk of focal neurological deficits, encephalopathy, seizures, and permanent cognitive dysfunction in brain-injured patients.<sup>105</sup> Further clinical trials are necessary to define the optimal BG range in this patient population, as case reports of neuroglycopenia and cerebral distress during insulin infusion, independent of peripheral hypoglycaemia, leave the pathophysiological importance of the rate of glucose change compared with the hypoglycaemic incident unclear.<sup>109</sup>

In the case of BG levels  $<3.9$  mM ( $70$  mg  $\text{dl}^{-1}$ ), Jacobi and colleagues<sup>105</sup> suggest immediately stopping the insulin infusion and administering titrated doses of  $10$ – $20$  g of hypertonic ( $50\%$ ) dextrose to avoid excessive replacement. BG measurement should be repeated after  $15$  min with additional dextrose as needed to maintain a BG level  $>3.9$  mM ( $70$  mg  $\text{dl}^{-1}$ ).<sup>105</sup> The ADA recommends instituting a hypoglycaemia protocol and suggests administering a  $15$ – $20$  g bolus of i.v. dextrose, checking BG level every  $5$ – $15$  min, and repeating dextrose boluses as indicated.<sup>29</sup>

### Medication

Insulin infusion is the medication of choice for glucose control in critically ill patients.<sup>2 29 110–112</sup> Subcutaneous insulin can be an alternative treatment for selected ICU patients who are clinically stable and have low insulin requirements<sup>105 113</sup> or when preparing the stabilized patient for transition to the ward. Such an approach must be individualized and might be influenced by hospital or unit policy (Table 10).

### Glucose monitoring

Critically ill patients can also suffer from hypoglycaemia in the absence of insulin treatment due to concomitant illness such as liver disease, immune compromise, and renal failure. Patients are also at risk for hypoglycaemia after interruption of caloric intake, with the use of vasoactive infusions, or with renal replacement therapy using bicarbonate-based replacement fluid in sepsis.<sup>114</sup> Arterial or venous whole blood sampling is recommended for BG analysis whenever available and particularly in patients suffering from shock, receiving vasopressor therapy, those with severe peripheral oedema, and those receiving prolonged insulin infusion.<sup>105</sup>

The Surviving Sepsis Campaign<sup>103</sup> and Jacobi and colleagues<sup>105</sup> propose a consensus recommendation based on limited data where BG is monitored every  $1$ – $2$  h during insulin infusion. Protocols that propose checking glucose every  $4$  h bear a  $>10\%$  risk of unrecognized hypoglycaemia.<sup>70 94</sup>

### Transition to ward or IMCU

Before discharge to the ward, the majority of stable ICU patients should be transitioned to a protocol-driven basal/bolus insulin regimen. This can be instituted before the insulin infusion is discontinued to avoid marked swings in BG.<sup>105</sup> Transition should be put on hold until there are no planned interruptions of nutrition, until peripheral oedema has resolved, and until the patient is off vasopressors. Whenever the BG target ( $<10$  mM,  $180$  mg  $\text{dl}^{-1}$ ) cannot be achieved by subcutaneous insulin, the regimen should be adjusted or the insulin infusion restarted.

Many hospitals are unable to implement insulin infusions on general floors or in the IMCU due to staffing policies. A basal/bolus regimen derives a benefit in type 2 diabetics requiring  $>0.5$  units  $\text{h}^{-1}$  of insulin and in non-diabetics requiring  $>1$  units  $\text{h}^{-1}$ .<sup>115</sup> Some institutions propose other cut-off values or even suggest the exclusion of SIH patients from such transition.<sup>115–120</sup> Calculation of basal and bolus insulin dosing requirements should be based on previous i.v. insulin dosing and concomitant carbohydrate intake. Most transitional models propose a combination of basal insulin, nutritional insulin, and correction insulin (Table 10).<sup>115–121</sup> Supplementary correction insulin (in the form of a sliding scale) is titrated according to long-acting insulin and basal-bolus orders. The routine sole administration of sliding-scale insulin to control BG on the ward, IMCU, or ICU is strongly discouraged because of increased GV, incidence of hypo- and hyperglycaemia,<sup>122</sup> and complications during hospitalization.<sup>29 111 123</sup>

### Ward

There is no clear evidence for specific BG goals in non-critically ill postoperative patients.<sup>29</sup> Patients treated with insulin should aim at a pre-meal BG  $<7.8$  mM ( $140$  mg  $\text{dl}^{-1}$ ) with random BG values  $<10$  mM ( $180$  mg  $\text{dl}^{-1}$ ), assuming that these targets can be safely achieved.<sup>29 123</sup> More stringent targets can be suggested in stable patients with previous tight glycaemic control.<sup>29</sup> Less stringent values might be appropriate in patients with severe co-morbidities.<sup>29</sup> Hence, for patients with terminal illness, limited life expectancy, or a high risk of hypoglycaemia, a higher BG target  $>11.1$  mM ( $200$  mg  $\text{dl}^{-1}$ ) might be reasonable.<sup>123</sup> The definition of hypoglycaemia does not differ based on patient acuity or physical location. Hypoglycaemia is recognized as a BG  $<3.9$  mM ( $70$  mg  $\text{dl}^{-1}$ ), which correlates with the threshold for the release of counter-regulatory hormones, and severe hypoglycaemia is defined as levels  $<2.2$  mM ( $40$  mg  $\text{dl}^{-1}$ ).<sup>29</sup>

Outside of the operating theatre and ICU, subcutaneous insulin is recommended and generally accepted as the standard method of insulin administration.<sup>123</sup> There is no study that evaluates IIT in patients on the general ward. Scheduled subcutaneous insulin should involve basal, nutritional, and correction components (with the latter two provided before meals) and should be accompanied by meals with a consistent amount of carbohydrate.<sup>123</sup>

Barriers to administering oral hypoglycaemic agents in postoperative inpatients include variability in caloric intake, ileus, and limited ability to titrate the drugs. Metformin, in

**Table 10** Concepts for transition from i.v. insulin therapy to subcutaneous insulin regimen. ICU, intensive care unit, BG, blood glucose, DM, diabetes mellitus, ADA, American Diabetes Association, TDD, total daily dose

	Donaldson and colleagues <sup>117</sup>	Furnary and Braithwaite <sup>116</sup>	O'Malley and colleagues <sup>115</sup>	Ramos and colleagues <sup>118</sup>	Avanzini and colleagues <sup>120</sup>	Magaji and colleagues <sup>141</sup>
General requirements	Extubated, off vasopressors, intra-aortic balloon pump out, stable renal function, no oedema					
Indications for transition	<ul style="list-style-type: none"> <li>- Cardiac surgery</li> <li>- Many patients require perioperative insulin infusion</li> <li>- Many patients ready to transition on postop. day 1, tolerance of oral intake not essential</li> <li>- Major surgery</li> <li>- Most patients little need for meal-time bolus in first postop. days</li> <li>- Non-diabetics with insulin infusion <math>&gt;0.5</math> units <math>h^{-1}</math></li> </ul>	<ul style="list-style-type: none"> <li>- Taking liquids/regular meals</li> <li>- Diabetic diet</li> <li>- DM type 2 or hospitalization-related hyperglycaemia</li> <li>- Receiving <math>&lt; 2</math> units <math>h^{-1}</math> insulin infusion with BG <math>&lt;7.2</math> mM (130 mg <math>dl^{-1}</math>)</li> <li>- Basal insulin dose <math>&lt;48</math> units <math>h^{-1}</math> during insulin infusion</li> </ul>	<ul style="list-style-type: none"> <li>- DM type 2 on insulin as outpatient</li> <li>- DM type 2 with recent mean insulin infusion rate of <math>&gt;0.5</math> units <math>h^{-1}</math></li> <li>- Stress hyperglycaemia or previously unrecognized DM if insulin infusion rate <math>&gt;1</math> units <math>h^{-1}</math> or HbA1c above normal</li> <li>- Some institutions exclude all stress hyperglycaemia patients</li> </ul>	<ul style="list-style-type: none"> <li>- Patients on medications for diabetes</li> <li>- HbA1c <math>&gt;6\%</math></li> <li>- Patients with equivalent of <math>&gt; 60</math> mg of prednisone and insulin infusion rate <math>&gt;1</math> units <math>h^{-1}</math></li> <li>- Patients with stress hyperglycaemia regardless of insulin infusion rate: no transition to basal subcutaneous insulin</li> </ul>	<ul style="list-style-type: none"> <li>- Mean dose of insulin infusion in 24 h before transition <math>&lt;1.6</math> units <math>h^{-1}</math></li> <li>- BG coefficient of variation in 24 h before transition <math>&lt;11.9\%</math></li> </ul>	Patients eating reliably
Calculation of daily insulin dose	Last stable insulin infusion rate $\times 24 = 24$ h insulin dose	Average insulin infusion rate in 6–8 h interval while being NPO and receiving no i.v. dextrose: 6 h total dose $\times 4$ or 8 h total dose $\times 3$	TDD of insulin for 24 h full nutrition: (1) Mean insulin infusion rate per hour from last 6 to 8 h (2) Hourly rate $\times 24$ , then multiply by 0.7 or 0.8=safety-adjusted insulin dose	TDD=averaging hourly drip rate over prior 6 h multiplied - By 20 if taking full nutrition ( $>50\%$ of calories) - By 40 if taking minimal nutrition (NPO, $<50\%$ of calories)	Estimate of combined basal and nutritional subcutaneous insulin requirements - Average insulin infusion rate in last 12 h=mean hourly rate $\rightarrow$ multiplied by 24=daily insulin requirement	- Patient's hourly insulin infusion rate while NPO $\times 24 = 24$ h basal insulin dose during stress
Basal insulin	80% of 24 h insulin dose=first dose of glargine	Initial glargine dose=80% of the 24 h basal insulin requirement	Glargine or detemir - 40–50% of TDD	50% of TDD=first dose of glargine	Halve daily insulin requirement=basal insulin dose	Adjusted basal dose accounting for stress reduction= $2/3 \times 24$ h basal insulin dose during stress=units of glargine

Bolus (mealtime) insulin	Post-prandial BG >7.8 mmol litre <sup>-1</sup> (140 mg dl <sup>-1</sup> ): add 25% of daily dose of glargine as rapid-acting insulin with each meal	Initiation with first dietary trays, even if insulin infusion still running	Remainder of the TDD=scheduled nutritional insulin. Estimation of first dose: - 50% of the TDD as nutritional coverage, divided by 3 to determine mealtime bolus (hold if <50% of meal is eaten) - More conservative: 10–20% of basal dose for every meal	50% of TDD divided into - regular insulin every 6 h for patients on tube feeds OR - lispro (Humalog) before meals if tolerating oral diet Patients on minimal nutrition: hold 50% nutritional dose until full nutrition tolerated	Halve daily insulin requirement and split into: - 20% at breakfast - 40% at lunch - 40% at dinner	- Provide as soon as patients start eating - Depend on patients' caloric intake - Start with 10% of adjusted basal dose, given at each meal
Conversion protocol	Overlap first glargine dose with insulin infusion by several hours	Stop insulin infusion 2 h after first glargine dose	- Basal insulin at least 2 h before insulin infusion stops - Shorter lead time (30 min) possible if rapid-acting insulin is given with basal insulin	Basal insulin administration 2 h before insulin infusion stopped	Give first basal insulin dose 2 h before first meal and discontinuation of insulin infusion and i.v. dextrose.	- Continue insulin infusion at least 4 h after first glargine dose - Stop insulin infusion sooner when glargine and rapid-acting meal-time bolus are given
Monitoring BG measurements	- Adapt glargine every 24 h - Patients without previous DM and normal HbA1c: taper glargine by 20% of first dose per day and discharge without prescription - Patients with previous DM: maintain on glargine and mealtime insulin until discharge (transition glargine to previous outpatient therapy modified as required by HbA1c)	BG measurement at: Pre-prandially 2 h post-prandially bedtime 3.00 am Revise total 24 h dose daily Revise distribution of basal and prandial insulin daily to approach 50% basal and 50% prandial	Use carbohydrate counting to cover nutritional intake			- Increase mealtime boluses daily according to caloric intake



particular, should likely be restarted no earlier than 48 h after surgery when no renal insufficiency or nausea and vomiting are present.<sup>112 124</sup> Patients whose glycaemic status was well controlled before hospital admission, however, can usually transition to oral agents 1 or 2 days before discharge.<sup>29 111</sup> Patients on home insulin regimes should ideally resume their preadmission schedule at least 1 day before discharge.<sup>123</sup>

## Conclusion

Perioperative dysglycaemia in the adult surgical population is ubiquitous, and unfortunately often undiagnosed. The preponderance of evidence indicates that abnormal glucose homeostasis has an adverse effect on patient outcomes. Anaesthesiologists, as leaders of the 'surgical home' model, are perfectly poised to aid in the identification of these patients, initiate treatment, and facilitate referrals for postoperative care. Given the heterogeneous nature of this population, it is unlikely that one standard of perioperative glycaemic control is appropriate for all patients. Certainly, early identification coupled with timely intervention contributes to significant risk reduction. Although not clearly delineated, the desired level of intraoperative and postoperative glucose control rests somewhere between strict control and overt hyperglycaemia; the goal being adequate control and avoidance of hypoglycaemia. Future investigations will help identify specific perioperative glucose targets, especially in specialized surgical populations (i.e. cardiac, neurosurgical), while advances in monitoring and medications will make it easier to achieve specific glucose targets in individual patients. Closed-loop, continuous monitoring, and management systems with smart alarms and clinical interfaces to enhance glycaemic control are likely to be forthcoming, but are currently not clinically available.<sup>125</sup>

## Authors' contributions

J.J.S., A.K.L., and D.B.C.: research, writing, and revision of the paper.

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