CURRENT OPINION

The impact of glycaemic variability on the surgical patient

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Purpose of review

Diabetes is the most prevalent long-term metabolic condition and its incidence continues to increase unabated. Patients with diabetes are overrepresented in the surgical population. It has been well recognized that poor perioperative diabetes control is associated with poor surgical outcomes. The outcomes are worst for those people who were not recognized as having hyperglycaemia.

Recent findings

Recent work has shown that preoperative recognition of diabetes and good communication between the clinical teams at all stages of the patient pathway help to minimize the potential for errors, and improve glycaemic control. The stages of the patient journey start in primary care and end when the patient goes home. The early involvement of the diabetes specialist team is important if the glycated haemoglobin is more than 8.5%, and advice sought if the preoperative assessment team is not familiar with the drug regimens. To date the glycaemic targets for the perioperative period have remained uncertain, but recently a consensus is being reached to ensure glucose levels remain between 108 and180 mg/dl (6.0 and 10.0 mmol/l). There have been a number of ways to achieve these – primarily by manipulating the patients' usual diabetes medications, to also allow day of surgery admission.

Summary

glycaemic control remains an important consideration in the surgical patient.

INTRODUCTION

The most recent estimates from the International Diabetes Federation suggest that the number of people worldwide who have diabetes mellitus is about 387 million, with this number predicted to rise to almost 600 million by 2035 [1]. Over 90% of these people have type 2 diabetes mellitus. Diabetes accounts for up to 10% of heath care expenditure in developed nations, these huge costs are related to the excess number of hospital admissions [2]. Inpatients with diabetes have significantly longer bed occupancy rates, as well as higher mortality rates, than those without diabetes, admitted for the same conditions [3]. In surgical patients, the length of hospital stay is 45% higher than those without diabetes, with general surgical and orthopaedic patients often having the longest lengths of stay [2,4]. A significant proportion of patients with diabetes mellitus are often inappropriately denied day case surgery and this may contribute to the increased length of stay [5].

The mortality of surgical patients with diabetes is twice that of those without [6], and some of the causes are shown in Table 1. Although it has been recently suggested that following guidelines is associated with improved outcomes for patients with diabetes [7,8], surgical patients with diabetes mellitus cost the heath service more money.

THE SURGICAL PATHWAY FOR PEOPLE WITH DIABETES

There is usually a well trodden pathway for the elective surgical patient: primary care; referral to surgical outpatients; the preoperative assessment

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KEY POINTS

- Dysglycaemia – hypo and hyperglycaemia – are associated with poor surgical outcomes and all attempts should be made to maintain glucose levels between 108 and 180 mg/dl (6.0 and 10.0 mmol/l) during the perioperative period.
- Preoperative HbA1c values of more than 69 mmol/mol (8.5%) are associated with increased risk of poor surgical outcomes and elective surgery should be deferred until this can be safely achieved.
- The diabetes specialist team should be involved at all stages of the patient pathway, which starts in primary care, and encompasses the surgical outpatients, preoperative assessment clinic, hospital admission, theatres and recovery, postoperative recovery, and discharge.
- Day of surgery admission should be encouraged and can be safely achieved by manipulation of the patients' usual diabetes medication.

clinic; admission to hospital; surgery and post-anesthesia care unit; postoperative recovery; and discharge from hospital [9]. The first three parts of the pathway are not possible for emergency patients but diabetes remains an important consideration. Identification of patients with diabetes and communication between staff members, including the patient, at each stage of the pathway is the best way of ensuring patient safety. Where necessary, the diabetes specialist team should be involved, because it has been shown that their expertise helps to reduce length of stay [10,11]. They are of most help when trying to achieve glycaemic optimization at each stage of the care pathway. In the UK, the recommended target glycated haemoglobin (HbA1c) is less than 69 mmol/mol (8.5%) before elective surgery, where it is well tolerated to do so [12■■], and the recommended blood glucose range, whereas in hospital is 108–180 mg/dl (6.0–10.0 mmol/l), with an acceptable range of 108–216 mg/dl (6.0–12.0 mmol/l). The glucose range in the USA recommended by the American Association of Clinical Endocrinologists and the American Diabetes Association for inpatients is 100–180 mg/dl (5.9–10.0 mmol/l) [2].

Table 1. Possible causes of adverse outcomes for surgical patients with diabetes mellitus

Failure to identify patients with diabetes
Lack of institutional guidelines for management of diabetes
Lack of knowledge of diabetes and it's management by medical and nursing staff
Hypo and hyperglycaemia
Multiple comorbidities, including microvascular and macrovascular complications
Complex polypharmacy, including misuse of insulin
Inappropriate use of intravenous insulin
Management errors when converting from the intravenous insulin to usual medication
Perioperative infection

LONG-TERM GLYCAEMIC CONTROL AND OUTCOME

Poor preoperative glycaemic control, as measured by elevated HbA1c concentrations, has been associated with poor surgical outcomes for emergency and elective patients in many surgical specialities [6,13–17,18■]. These include increased rates of postoperative complications such as surgical site infection, systemic infections, urinary tract infection and lower respiratory tract infection, acute kidney injury, acute coronary syndrome, pneumonia, admission to intensive care, prolonged length of stay, and death. However, although there is considerable evidence to show that poor preoperative glycaemic control, as defined by an elevated HbA1c, is associated with a poor outcome, there are few data to show that decreasing it is associated with improved outcomes [19]. A recent systematic review questioned the relationship between glycaemic control, as measured by HbA1c, and poor outcomes. The authors concluded that the relationship is not clear but conceded that the studies were predominantly retrospective, contained small patient numbers and were relatively heterogeneous. Overall, the quality of the studies was poor [20■].

IMMEDIATE PREOPERATIVE GLYCAEMIC CONTROL AND OUTCOME

Two seminal studies examined the effects of blood glucose concentrations on the day of surgery prior to incision [6,17]. Both studies demonstrated that immediate preoperative hyperglycaemia in patients with documented and undocumented diabetes was a poor prognostic indicator. Kwon and colleagues [17] defined hyperglycaemia as glucose values greater than 180 mg/dl (10.0 mmol/l).

INTRAOPERATIVE GLYCAEMIC CONTROL IN CARDIAC SURGERY

Most work on intraoperative glycaemic control and outcome has been undertaken in cardiac surgery. Although these patients represent a small proportion of all patients undergoing surgery, there have been some important findings. Furnary and colleagues [21] showed that glycaemic control using an intravenous insulin infusion to achieve perioperative blood glucose values less than 200 mg/dl (11.1 mmol/l) was associated with significantly fewer complications compared with historical controls. Lazar and colleagues [22] in a prospectively randomized study found, that achieving a blood glucose concentration between 125 and 200 mg/dl (7.0–11.1 mmol/l) with intravenous glucose, insulin, and potassium was associated with significantly fewer complications than standard therapy with subcutaneous insulin, when the blood glucose was greater than 250 mg/dl (13.9 mmmol/l). These included atrial fibrillation; shorter length of stay; fewer wound infections; less recurrent ischaemia, and death.

Although preventing significant hyperglycaemia in cardiac surgery has been shown to be beneficial, very tight glycaemic control, that is, glucose concentrations of 80–100 mg/dl (4.5–5.3 mmol/l) is associated with an increased risk of hypoglycaemia [23]. In a recent study, patients with and without a diagnosis of diabetes were randomized to conventional glycaemic control of 140–180 mg/dl (7.8–10.0 mmol/l) or tight glycaemic control of 100–180 mg/dl (5.6–7.7 mmol/l) [24]. Overall, tight glycaemic control did not significantly reduce the rate of postoperative complications, but a subgroup analysis showed that the patients in the tight glycaemic control group, who did not have a prior diagnosis of diabetes mellitus, had a significantly lower rate of complications [24]. Similar beneficial effects were found in cardiac surgical patients who were not diagnosed with diabetes mellitus before surgery when glucose values were maintained between 79 and 110 mg/dl (4.4–6.1 mmol/l) perioperatively [25].

In 2009, the Society of Thoracic Surgeons in the USA reviewed the available literature for adult cardiac surgery and blood glucose management and concluded that glucose concentrations over 180 mg/dl (10.0 mmol/l) should be treated with an intravenous insulin infusion [26]. There have been no subsequent publications to suggest that these recommendations need to be altered.

INTRAOPERATIVE GLYCAEMIC CONTROL IN NONCARDIAC SURGERY

For many years there has been a consensus that hyperglycaemia should be treated in cardiac surgery. The evidence in the noncardiac surgical patient is less convincing. Over the past 10 years, retrospective studies in liver transplant surgery, colorectal surgery, as well as vascular and joint arthroplasty surgery have been published that show that intra and postoperative hyperglycaemia (defined as >200 mg/dl (11.1 mmol/l)), is associated with significantly poorer outcomes [6,16,17,27–36]. There were methodological weaknesses in these studies and treatment protocols varied greatly. The complications associated with hyperglycaemia included: surgical site infection, systemic infections, further surgery, acute kidney injury, acute coronary syndromes, increased length of stay, and death. In several studies, significantly higher rates of complications were found at glucose concentrations lower than 200 mg/dl (11.1 mmol/l).

MANAGEMENT OF HYPERGLYCAEMIA IN CRITICALLY ILL PATIENTS

In 2001, van den Berghe and colleagues [37] published a landmark paper which showed that using intensive insulin therapy in a surgical intensive care unit aiming for glucose concentrations of 80–110 mg/dl (4.5–6.1 mmol/l) significantly reduced mortality. Post-hoc analysis revealed that although the most favourable results were achieved with a range of 80–110 mg/dl (4.5–6.1 mmol/l), values below 150 mg/dl (8.3 mmol/l) also improved outcomes. This seminal paper was instrumental in shaping the Surviving Sepsis Guidelines [38] which suggested that in the severely septic patient blood glucose concentrations should be kept below 150 mg/dl (8.3 mmol/l) [38]. The guidelines acknowledged the risk of hypoglycaemia with this target value.

In 2006, a further study by van den Berghe and colleagues [39] in a medical ICU showed no difference in mortality, but less morbidity in the tight glycaemic control group. It was recognized that intensive insulin therapy may lead to fatal hypoglycaemia.

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) was stopped early because it showed that aiming for a blood glucose range of 80–110 mg/dl (4.5–6.1 mmol/l) was harmful compared with 180–200 mg/dl (10.0–11.1 mmol/l) [40]. Two further relevant studies were published in 2009, The Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE–SUGAR) and the Glucontrol studies [41,42]. The NICE-SUGAR was a large international randomized trial, and it demonstrated that aiming for a blood glucose of 81–108 mg/dl (4.6–6.0 mmol/l) was associated with a significantly greater mortality than keeping the blood glucose less than 180 mg/dl (10.0 mmol/l) [41]. The Glucontrol study was prematurely stopped because of multiple protocol violations, but it found that aiming for blood glucose of 80–100 mg/dl (4.5–5.6 mmol/l) was associated hypoglycaemia [42]. In 2012, the NICE-SUGAR investigators published follow-up data that demonstrated a 'dose – response relationship' between the degree of hypoglycaemia and risk of death [43].

The 2012 edition of the Surviving Sepsis Guidelines states that insulin should only be started once two consecutive glucose concentrations are more than 180 mg/dl (10.0 mmol/l) [44]. Insulin should be given to obtain blood glucose values 180 mg/dl or less (10.0 mmol/l), rather than an upper limit of 110 mg/dl or less (6.1 mmol/l). Fully automated, closed loop systems delivering a continuous infusion of subcutaneous or intravenous insulin enable better glycaemic control to be achieved [45].

STRESS HYPERGLYCAEMIA AND UNDIAGNOSED DIABETES

It has been estimated that a large proportion of people with type 2 diabetes mellitus are unaware that they have the condition. Thus, there are at least two reasons why an individual may have high blood glucose concentrations when presenting for surgery – they have undiagnosed diabetes mellitus, or they have 'stress hyperglycaemia'.

Undiagnosed diabetes

As described previously, patients who were hyperglycaemic preoperatively and on no treatment had a worse outcome than patients with treated diabetes who had similar preoperative blood glucose values [6,17]. The inference is that these patients had undiagnosed diabetes, and that treatment is protective. Whether performing random blood glucose measurements, or HbA1c, routinely during the preoperative assessment of patients at high risk of undiagnosed type 2 diabetes mellitus is beneficial has yet to be determined. Currently, it is not recommended in the UK [46].

Stress hyperglycaemia

Stress hyperglycaemia is an integrated physiological response to acute illness and results from the production of several 'counter-regulatory' hormones – in particular cortisol, growth hormone, and catecholamines – that raise glucose concentrations [47]. Drugs such as glucocorticoids that alter insulin sensitivity may also contribute to the ensuing hyperglycaemia [48]. Hyperglycaemia most often occurs in obese individuals, those with a family history of type 2 diabetes mellitus or a personal history of gestational diabetes. The distinction between known diabetes and 'stress hyperglycaemia' is important because the data suggest that if diabetes is identified before surgery then the outcome for people with diabetes may be no different – or indeed may be better – than for those without diabetes [17,49]. The reasons for this are unclear but may be related in part to the increased vigilance of patients with diabetes mellitus, for example, the frequent measurement of blood glucose concentrations.

A study of over 330 patients admitted to intensive care without a previous diagnosis of diabetes mellitus found that 73% developed hyperglycaemia during their intensive therapy unit stay. At follow-up 8 months later, these patients had an oral glucose tolerance test; 35% had dysglycaemia, with 7% having overt diabetes [50]. Thus, stress hyperglycaemia should not be considered a 'benign' condition because of the potential long-term consequences.

HYPOGLYCAEMIA AND OUTCOMES

The greatest risk of treating diabetes is the occurrence of hypoglycaemia. Hypoglycaemia is defined as 'an event during which typical symptoms of hypoglycaemia are accompanied by a measured glucose concentration less than 70 g/dl (3.9 mmol/l)' [51]. Severe hypoglycaemia is defined as less than 40 mg/dl (<2.2 mmol/l), or a blood glucose that is low enough for the individual to require third party assistance. The danger of hypoglycaemia is neuroglycopaenia resulting in cognitive impairment, seizures, coma, and ultimately death, because glucose is the obligatory metabolic fuel of the brain. These effects begin to occur at approximately 50 mg/dl (2.8 mmol/l).

Hypoglycaemia is a common occurrence in hospitalized patients. A study of inpatients with diabetes in the UK found that 22% had one or more hypoglycaemic episodes over the previous 7 days of their stay (blood glucose measurement of 70 mg/dl (3.9 mmol/l) or less) [52]. In the USA, the reported prevalence of hypoglycaemia in inpatients is from 3 to 29% [53–56]. The risk factors for developing inpatient hypoglycemia include older age, presence of comorbidities, diabetes, increasing number of antidiabetic agents, tight glycaemic control, septic shock, renal insufficiency, mechanical ventilation, and severity of illness [57,58]. Hypoglycaemia is independently associated with increased mortality [41,43,59].

Hospital acquired hypoglycaemia results from a combination of an absolute or relative insulin excess with concurrent defects in the defences against a decreasing blood glucose. Insulin excess is often because of the pharmacokinetic imperfections of insulin preparations and insulin secretagogues in the context of altered diet, drug interactions, altered sensitivity to insulin, and insulin clearance. The physiological defences against a falling blood glucose are the:

(1) Ability to rapidly reduce insulin secretion.
(2) Ability to rapidly secrete glucagon.
(3) Ability to rapidly increase circulating epinephrine. The loss of this ability is associated with 'hypoglycaemia unawareness'.
(4) Ability to autonomously recognise symptoms of hypoglycaemia and ingest carbohydrates.

These defences are often defective or attenuated in a patient with diabetes mellitus.

Several key studies have shown the dangers of severe hypoglycaemia when attempting to achieve tight glycaemic control of less than 110 mg/dl (6.1 mmol/l) [40,41,60–62].

It is salutary to note that the US Food and Drug Administration allows a 15% margin of error for glucose meters at concentrations below 100 mg/dl (5.6 mmol/l). Thus a measured concentration of 72 mg/dl (4.0 mmol/l) will have an actual value between 61 mg/dl and 83 mg/dl (3.4 and 4.6 mmol/l). Many other factors commonly found in surgical patients can also affect the measurement: poor peripheral perfusion, anaemia, increased bilirubin and uric acid, and drugs such as paracetamol, dopamine, and mannitol [63].

Although hypoglycaemia is defined as less than 70 mg/dl (3.9 mmol/l), there is considerable evidence to show that in hospitalized patients aiming for blood glucose values less than 110 mg/dl (6.1 mmol/l) is harmful.

TARGET BLOOD GLUCOSE CONCENTRATIONS

What should the glucose targets be for patients undergoing surgery? Over the past 20 years, there have been several popular regimens:

(1) Tight glycaemic control with a target glucose concentration of 80–110 mg/dl (4.4–6.1 mmol/l).
(2) Prevention of hypoglycaemia, that is, keeping blood glucose at more than 108 mg/dl (6.0 mmol/l).
(3) Loose glycaemic control of 72–216 mg/dl (4.0–12.0 mmol/l).

The recent 2013 guideline by a working group of the American Diabetes Association and the Endocrine Society stated 'the glycaemic target established for any given patient should depend on the patient's age, life expectancy, comorbidities, preferences, and an assessment of how hypoglycaemia might impact his or her life' [64]. However, the surgical, medical, nursing, and anaesthetic staff looking after the surgical patient with diabetes all need more definitive advice to promote consistently high-quality and safe care.

In his landmark paper on the perioperative management of diabetes, Alberti stated that the target blood glucose intraoperatively should be 90–180 mg/dl (5.0–10.0 mmol/l) [65]. He based his rationale on 'common sense'; recognising the dangers of hypoglycaemia and hyperglycaemia. The 2015 UK guidelines suggest an ideal target range of 108–180 mg/dl (6.0–10.0 mmol/l) [66▪▪]. The American guidelines published in 2010 and 2012 on inpatient glycaemic control recommended an upper limit of 180 mg/dl (10.0 mmol/l), and that glucose levels less than 100 mg/dl (6.1 mmol/l) should trigger a reassessment of antidiabetic therapy [2,67].

PERIOPERATIVE METHODS OF MAINTAINING THE BLOOD GLUCOSE IN THE TARGET RANGE

The achievement of a safe blood glucose concentration (i.e. no risk of neurological harm from hypoglycaemia, and a reduced risk of hyperglycaemia-associated complications) is the 'holy grail' of those caring for patients with diabetes undergoing surgery. Various strategies have been employed, each with their own advantages and disadvantages and possible complications.

The glucose, insulin, and potassium regimen (Alberti Regimen)

Alberti suggested that the glycaemic control could be safely achieved by infusing 500 ml of 10% glucose at 100–125 ml/h with 10 units of soluble insulin and 1 g of potassium chloride. If the blood glucose value was outside the range of 90–180 mg/dl (5.0–10.0 mmol/l), a new bag of glucose and potassium was administered with a different amount of insulin [65]. Capillary blood glucose (CBG) concentrations should be checked 1–2 hourly on this regimen. This was a simple and reliable method of achieving glycaemic control, and is still used in some hospitals because of its inherent safety.

The variable rate intravenous insulin infusion

The administration of glucose, insulin and potassium in one bag (GIK regimen) was very labour intensive and was superseded in many centres by the

Table 2. Possible complications of the variable rate intravenous insulin infusion

Delayed commencement, causing DKA
Incorrect programming causing hypoglycaemia/hyperglycaemia
Incorrect connections causing hypoglycaemia/hyperglycaemia
No one way antisiphon valves causing hypoglycaemia or hyperglycaemia
Insufficient or inadequate measurement of CBG
Premature discontinuation of intravenous glucose but with continuation of the intravenous insulin infusion causing hypoglycaemia
Premature disconnection, without prior administration of sufficient and appropriate insulin, in a patient with type 1 diabetes mellitus resulting in DKA
Delayed disconnection from the variable rate intravenous insulin infusion because staff are unfamiliar with the practice
Hyponatraemia because of the lack of sodium in the i.v. fluid
Hypokalaemia because of inadequate potassium in the i.v. fluid
Attempts to achieve tight glycaemic control (e.g. CBG 4.0–6.0 mmol/l), with increased risk of hypoglycaemia

CBG, Capillary blood glucose; DKA, diabetic ketoacidosis.

Table 3. Criteria for the surgical patient with diabetes mellitus to have glucose controlled by manipulation of normal medication

Patient/surgical factors
Adequate glycaemic control (HbA1c < 69 mmol/mol or < 8.5%)
Stable and nonseptic
Does not require immediate or urgent surgery
Ability to understand instructions
No expected surgical reason for postoperative starvation/ileus
Institutional factors
Ability to reliably give the patient a time for surgery so that the patient will only miss one meal
Ability to prioritise the patient on the operating list
Availability of a trained member of staff to discuss manipulation of drugs with the patient, and that the patient is able to follow these instructions
Ability to perform safe discharge of the patient and ensure that the patient understands when to seek medical advice (i.e. follow 'sick day rules')

simultaneous administration of glucose at a fixed rate and insulin at a variable rate according to the blood glucose concentration. This regimen was initially known in the UK as a 'sliding scale', but is now referred to as the 'variable rate intravenous insulin infusion' (VRIII). The VRIII is cumbersome, needs dedicated intravenous access, and is also labour intensive because (CBG) concentrations should be checked hourly on this regimen and the fluid running with the regimen would need to change depending on the glucose concentration. Furthermore, data from local and national audits show that the VRIII does not reliably control the blood glucose and is associated with hypoglycaemia (Table 2). Despite these drawbacks, the VRIII is the preferred method of treating the surgical patients with diabetes mellitus who have prolonged starvation.

'Sliding scale' subcutaneous insulin

Many centres chose to use intermittent boluses of subcutaneous insulin to maintain glycaemic control perioperatively. This regimen was also called a 'sliding scale'. Guidelines do not recommend the prolonged use of subcutaneous sliding scale insulin therapy because it is ineffective in most patients and potentially dangerous in those with type 1 diabetes mellitus [2,68,69▪].

Perioperative manipulation of drugs

The advent of better diabetes drugs, better long-term glycaemic control, less physiologically stressful surgery, better control of postoperative nausea and vomiting, and shorter perioperative starvation periods have provided a novel strategy for maintaining glycaemic control – manipulation of the patient's normal diabetes medication [66▪▪]. This regimen is only possible in carefully selected individuals (Table 3). It overcomes many of the disadvantages of the VRIII and the GIK regimen and allows both day surgery and day of surgery admission. Moreover, for those patients who are likely to miss only one meal, their drugs can be manipulated as recommended by the UK Joint British Diabetes Societies [66▪▪]. Similar recommendations have been devised by the Society for Ambulatory Anaesthesia in the USA [70]. Currently, there is limited evidence to support these recommendations [71,72].

Continued use of a continuous subcutaneous insulin infusion pump

An increasing number of patients with diabetes use a subcutaneous insulin infusion pump. By manipulating the rate of insulin infusion, for example, reducing the basal infusion by approximately 20%, and following specified guidelines, with hourly CBG concentration measurements they can continue to be used perioperatively (Table 3) [73,74].

CONCLUSION

The care of surgical patients with diabetes needs to improve. Identification of patients with diabetes at an early stage, with pre and perioperative optimization of glycaemic control will minimize postoperative complications. Patients need to be involved in decisions about their care. Knowledge of current developments in the treatment of diabetes mellitus and interdisciplinary communication are essential for ensuring patient safety.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest

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