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REVIEW ARTICLE

Pre-operative optimisation of the surgical patient with diagnosed and undiagnosed diabetes

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Introduction

Diabetes mellitus is the most prevalent long term metabolic condition. Diabetes mellitus is a multisystem disorder that is characterised by chronic hyperglycaemia. It can be classified into the following general categories [1]:

1. Type 1 diabetes mellitus. This is due to β-cell destruction and usually leads to absolute insulin deficiency;
2. Type 2 diabetes mellitus. This is due to a progressive insulin secretory defect coupled with insulin resistance;
3. Gestational diabetes mellitus. This is diabetes diagnosed during pregnancy that may or may not resolve after delivery;
4. Other. This covers all the conditions that may predispose to hyperglycaemia e.g. diseases of the pancreas, glucocorticoid use, and monogenic disorders causing maturity onset diabetes of the young.

There are recent data to suggest that there are several different sub-classes of diabetes [2]. However, there are currently not enough data on peri-operative diabetes care to understand the implications of these subtypes on the outcomes of surgery.

The prevalence of diabetes is increasing. The most recent estimates from the International Diabetes Federation suggest that the number of people worldwide who have diabetes mellitus is about 425 million, i.e. 1 in 11 adults. This number is predicted to rise to almost 700 million by 2045 [3]. Over 90% of these people have type 2 diabetes mellitus. In the UK it is estimated that there are 3.8 million people with diabetes (8.6% of the adult population), this includes an estimated 940,000 people who have undiagnosed diabetes [4]. Diabetes accounts for up to 10% of heath care expenditure in developed nations, and these huge costs are related in part to the excess number of hospital admissions [5]. People with diabetes (both diagnosed and undiagnosed) have: a significantly longer hospital length of stay; more major complications ; a higher requirement for post-operative critical care admission; a higher requirement for post-operative ventilation; and higher mortality rates and episode costs compared to people without diabetes admitted for the same conditions [6,7]. In surgical patients, the length of hospital stay is up to 45% higher than those without diabetes, with general surgical and orthopaedic patients often having the longest lengths of stay [5,8]. In addition, 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 [9]. The mortality of surgical patients with diabetes is twice that of those without [10]; some of the causes for this are shown in Table 1. There is now increasing evidence that diabetes is a modifiable risk factor and that the care of the surgical patient with diabetes and pre-diabetes can be optimised, with a subsequent decrease in complications and mortality. It is therefore imperative that a consultation request by primary care for a surgical opinion mentions diabetes in the referral letter; a recent study showed that the presence of diabetes was not included in over 22% of all referral letters for people with the condition [11].

Pre-diabetes and Undiagnosed diabetes

Pre-diabetes is the disorder where there is hyperglycaemia without the accepted criteria for diabetes and is seen as precursor to diabetes. Pre-diabetes is diagnosed by either: a marginally elevated glycated haemoglobin (HbA1c) concentration; an impaired fasting glycaemia; or an impaired glucose tolerance. The diagnostic criteria for prediabetes do not describe the same populations, but they do overlap [12]. Depending on the organisation, the definitions are different. Table 2 shows the two most widely used criteria – from WHO and American Diabetic Association (ADA) for the diagnosis of diagnosis diabetes and pre-diabetes.

It is worth explaining the significance of glycated haemoglobin. Glycated haemoglobin reflects the average plasma glucose levels that the haemoglobin molecule has been exposed to over the preceding three months. It is used to diagnose diabetes and prediabetes, and to measure response to treatment. In 2011, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units ($mmol.mol^{-1}$) became the universally accepted units; the Diabetes Control and Complications Trial (DCCT) unit (%) is still in use despite being outmoded.

Undiagnosed diabetes is the condition in which the patient has diabetes but is yet to be diagnosed. The International Diabetes Federation currently estimates that worldwide just over 210 million people have undiagnosed diabetes. [3]. This represents half of all people with diabetes. In the United Kingdom, in 2014 Public Health England estimated that the prevalence (95%CI) of pre-diabetes in the general population was 10.7% (10.2–11.1%); the prevalence (95%CI) of undiagnosed diabetes was 2.3% (2.1–2.6%); and the prevalence (95%CI) of diagnosed diabetes was 5.2% (4.9–5.5%) [13]. Despite this, the National Institute for Health and Care Excellence does not currently recommend screening for diabetes in the 'at risk' surgical population [14]. This is despite there being evidence to suggest that undiagnosed diabetes mellitus is a greater risk factor for harm than diagnosed diabetes mellitus in the surgical population [10,15]. It has been argued that this is a missed opportunity to improve surgical outcomes [16].

In a recently published single centre Australian prospective study of patients aged >54 years undergoing inpatient surgery, it was demonstrated that of 7565 patients, 2047 (27%) patients had diabetes, as defined as HbA1c>48 mmol.mol^{-1} (6.5%); 2825 (37%) had pre-diabetes, as defined as a HbA1c of 39-47 mmol.mol^{-1} (5.7%-6.4%), and only 2457 (32%) patients were normoglycaemic. In addition, 2825 patients were diagnosed with pre-diabetes, and 236 patients (3% of the total study population) were found to have undiagnosed diabetes mellitus [7].

Table 3 shows a list of characteristics that should lead to a person to being screened for diabetes before referral for surgery. If any person is found to have undiagnosed diabetes mellitus, the appropriate treatment should be commenced. It is recommended that people with type 2 diabetes mellitus have treatment commenced or increased if the HbA1c exceeds 58 mmol.mol^{-1} (7.5%), whether surgery is planned or not [17].

Diabetes and surgical outcome

There are data from several surgical specialities to show that poor pre-operative glycaemic control (defined as either elevated blood glucose or HbA1c concentrations) is associated with harm [7,18-25]. However, increasingly data have suggested that it is those people who have previously undiagnosed hyperglycaemia who have the worst outcomes [10,15,26]. It may well be that this is because a known diagnosis of diabetes will almost always mean that a health care professional will observe and monitor the patient more often, if only to have a bedside capillary glucose measurement taken, and at such time, it may be noticed if the patient is becoming more unwell. This is described in a recent study that showed that the higher the pre-operative HbA1c, the more frequently capillary glucose concentrations were measured, as well as a greater likelihood of going onto an intravenous insulin infusion [27]. If an individual's glycaemic status is not known, they are likely to be observed less often. There is work to show poor surgical outcomes occur when the HbA1c concentration is raised, but still within the non-diabetic range; this association begins 43 mmol/mol (6.0%) [28,29]. There are however currently no prospective studies examining surgical outcome after randomising patients with poor glycaemic control to either no diabetes treatment or to diabetes treatment. In addition, this study may never occur as it may be deemed unethical to randomise patients with diabetes to no treatment. Thus, whilst it may seem 'intuitive' to optimise pre-operative HbA1c concentrations, there are few data to support this [30]. The exceptions to this are cardiac and liver transplant surgery [31,32]. There are also data to support improving glucose control to reduce surgical site infections [33].

Pre-operative glycaemic optimisation

Given that the epidemiological data suggest that 'good' pre-operative glycaemic control is associated with a lower risk of post-operative complications, it has been advocated that HbA1c concentrations should be optimised prior to an elective procedure, if it is safe to do so

[34]. For some patients, the risk of iatrogenic hypoglycaemia outweighs the benefits of better glycaemic control and pre-operative optimisation is not safely possible. For practical reasons suggestions from the UK advocate postponement of elective surgery only if the HbA1c is ≥ 69 mmol.mol^{-1} (8.5%) [34]; whilst the US Society for Ambulatory Anesthesia (SAMBA) suggests 53 mmol.mol^{-1} (7.0%) [35]. The National Institute for Health and Care Excellence now suggest that an HbA1c is a vital test that should be offered to all patients with diabetes if it has not been performed in the three months prior to the anticipated date of surgery [14]. Data from the Peri-operative Quality Improvement Programme (PQIP) 2017-2018 annual report demonstrated that, despite a pre-operative HbA1c being recommended in all patients with known diabetes, only 69% of such patients in that study had the pre-operative HbA1c performed [36].

Review of glycaemic control, and any subsequent glycaemic optimisation, should commence at the time of the referral for a surgical consultation and should continue at all stages of the patient journey: primary care; surgical outpatients; pre-operative assessment clinic; hospital admission; theatres and recovery; postoperative ward; and discharge home [34]. At all of these stages communication between the relevant staff and the patient is vital to help to ensure that optimal glycaemic control is achieved and maintained. Pre-operative glycaemic optimisation should be facilitated by either primary care or hospital specialists [34].

Pre-operative optimisation of comorbidity and drug therapy

Diabetes is a multisystem disease and is associated with several other comorbidities. These most frequently include cardiovascular disease, peripheral vascular disease, renal disease, hypertension, and obesity; 90% of adults with type 2 diabetes aged 16-54 years are overweight or obese [37]. Many of these co-existing conditions are also associated with increased surgical complications, and there is substantial evidence that patients with less severe comorbidity have better outcomes than those with severe and uncontrolled co-morbidity [38]. In addition, there is now emerging evidence that pre-operative optimisation of these associated conditions can lead to an improvement in outcome; many are discussed in detail in other sections of this journal supplement. Furthermore, the peri-operative strategies that are used to manage the associated conditions are changing and are associated with less morbidity. For example, The BRIDGE trial demonstrated that peri-procedural interruption of warfarin, for atrial fibrillation, with no anticoagulant bridging was not inferior to low molecular heparin bridging for the prevention of arterial thromboembolism, but decreased the risk of peri-procedural major bleeding [39].

The National Institute for Health and Care Excellence has produced many clinical guidelines for the optimisation of diabetes and its associated conditions [14,17,40-44]. However it is being increasingly realised that these guidelines often only consider the disease in isolation. This has the unintended consequence of potentially causing either drug-disease interactions or drug-drug interactions if medical practitioners apply the recommendations from the guidelines in isolation and do not consider the co-existing morbidity and polypharmacy. Pre-operative optimisation of the surgical patient with diabetes therefore demands careful scrutiny and optimisation/rationalisation of the existing medication to reduce the potential of peri-operative adverse drug events including: hypotension; bleeding; bradycardia; ventricular arrhythmias; altered plasma concentrations and hypo/hyperkalaemia caused by drug-disease or drug-drug interactions [45].

Prevention of peri-operative dysglycaemia

It has been demonstrated that both peri-operative hypoglycaemia and hyperglycaemia are associated with harm and death. Hypoglycaemia is often defined as a capillary blood glucose <4.0 $mmol.l^{-1}$ and severe hypoglycaemia is defined as a capillary blood glucose <3.0 $mmol.l^{-1}$ [46]. There are now data to demonstrate that hospital length of stay and increased risk of death actually occurs with a capillary blood glucose ≤4.0 $mmol.l^{-1}$ [47,48]. In addition, studies in which tight glycaemic control (4.5-6.0 $mmol.l^{-1}$) using intensive insulin therapy has been compared with a liberal target of 8.0-10.0 $mmol.l^{-1}$ have showed increased harm in the former group [49]. Therefore, the UK peri-operative guidelines now recommend that the lowest acceptable peri-operative capillary blood glucose on those with glucose lowering medication should be 6.0 mmol.l^{-1}, with the US guidelines suggesting reconsideration of treatment at 5.6 mmol.l^{-1} [5,34,50]. Because of the data suggesting that the treatment for hyperglycaemia is associated with harm, many societies and guidelines suggest treating inpatient hyperglycaemia only once the capillary blood glucose is above 10.0 mmol.l^{-1} [5,34,50]. Thus, there is a universal consensus that the optimal peri-operative target zone is approximately 6.0-10.0 mmol.l^{-1} [5,34,50-52]. This target is almost identical to the range recommended by Alberti in 1979, who suggested 5.0-10.0 mmol.l^{-1} [53]. In addition, the UK guidance recognises the dangers of glucose lowering medication and suggests that an upper limit of 12.0 mmol.l^{-1} may be acceptable [34].

As well hyperglycaemia predisposing the patient to both infective and non-infective complications, the patient with type 1 diabetes mellitus is also prone to diabetic ketoacidosis. Hospital-acquired diabetic ketoacidosis is defined as a patient developing diabetic ketoacidosis once in hospital for another reason, makes up almost 8% of all cases of diabetic ketoacidosis, and is the thus its third commonest cause [54]. At present the exact incidence of hospital acquired diabetic ketoacidosis in the surgical population is unknown. It is anticipated that the current National Confidential Enquiry into Patient Outcome and Death will be able to provide more data. The UK guidelines suggest the continuation of basal insulin, albeit at a reduced dose to prevent this highly undesirable complication [34,50].

In addition to identifying patients with previously undiagnosed hyperglycaemia, there are several strategies to prevent peri-operative dysglycaemia. These are summarised in Table 4. Precise details on the exact implementation of these strategies are beyond the scope of this article but have been previously published [50].

The unifying aspect for the successful implementation of all of these strategies is meticulous pre-operative assessment by staff with expertise in the pre-operative management of diabetes. Effective communication with the patient and the ward staff on the chosen management plan is vital. The diabetes drugs must be safely prescribed, and to facilitate safe day of surgery admission, it is recommended that these drugs are prescribed in the pre-operative assessment clinic. In addition, treatment in the event of both hypoglycaemia and hyperglycaemia should be prescribed at the per-operative assessment clinic, so that dysglycaemia can be managed if required from the moment of hospital admission

Safe use of insulin

Insulin remains one of the most frequently mis-prescribed and mis-administered drugs [55]. These medication errors include the wrong dose; or at the wrong time; or an inappropriate omission of a dose. It remains important to prescribe the correctly named insulin. Insulin should be prescribed by the complete brand name – including the strength and origin (e.g. human, animal or analogue). Importantly, the word 'unit' should be written out in full, never abbreviated as 'u' [56]. The mode of administration should also be included – prefilled pen, needle and vial or cartridge. When in doubt, always ask for help from the diabetes team. Furthermore, when insulin is administered it should always be given using an insulin syringe – these allow for 1 unit increments to be given.

Unresolved issues

In this section we will deal with the topic of stress hyperglycaemia before looking ahead to the future of peri-operative diabetic management.

The term stress hyperglycaemia describes transient elevations in blood glucose in patients without a history of diabetes that occur during acute illness or stress [57]. Several observational studies have reported higher morbidity and mortality in surgical patients with newly-recognised hyperglycaemia when compared to those even with known diabetes [58,59]. In general surgery, the development of peri-operative hyperglycaemia is associated with up to a fourfold increase in complications and twice the risk of death compared to patients maintaining normoglycaemia; this risk begins with a capillary blood glucose ≥ 7.8 $mmol.l^{-1}$ [10]. In a recent US study, the incidence of stress hyperglycaemia was found to be 21%; there are currently no studies from the UK [60]. It is currently unknown whether it is the patients with prediabetes that develop stress hyperglycaemia. If this was the case, it would further strengthen the argument for pre-operative screening using HbA1c for all patients having major surgery. At present there are no pre-/peri-operative studies examining whether these patients can be identified or whether treatment can affect the outcome of stress hyperglycaemia. The work by Van den Berghe et al in critically ill patients suggests that amongst other strategies insulin therapy may have a role, but more work is required [61,62].

The future remains full of potential in the field of peri-operative glycaemic control. Data from the 2017-2018 Peri-operative Quality Improvement Programme showed that, amongst those participating hospitals, care of surgical patients with diabetes can be improved, and has been identified as the foremost national improvement opportunity for 2018-2019. [36]. These data show that diabetes is taking a more prominent position in peri-operative care than previously.

Although there are outcome studies currently going on in this area (e.g. the Optimising Cardiac Surgery ouTcomes in People with diabeteS (OCTOPus) trial – HTA project number 16/25/12 – Professor Richard Holt, personal communication), there remain few data on the outcomes and effects of intervention on those not known to have diabetes. Given the rising prevalence of obesity this is an important 'missing link' in the field.

There also needs to be more research about the epidemiology of stress hyperglycaemia, and its optimal treatment. The optimal agents/ strategies needed to prevent peri-operative dysglycaemia also remain to be determined. The ideal agents would not cause hypoglycaemia and would be safe to use at times of acute illness. The use of the sodium glucose co-transporter 2 inhibitors is associated with an increased risk of diabetic ketoacidosis and should be avoided during periods of acute illness and there continues to be concerns about the use of metformin in renal impairment. The peri-operative use of drugs acting on the incretin pathway, the dipeptidyl peptidase 4 inhibitors and the glucagon-like peptides, have shown promise in preventing peri-operative hyperglycaemia; however, their use may be limited by side effects, including nausea and vomiting [63]. Finally, the increasing use of technology may help to reduce the risk of dysglycaemia associated with insulin use, as well as reducing the impact on staff time. The use of ‘closed loop’ glucose sensors and insulin delivery devices has shown promise in early trials in the inpatient population [64-66]. However, because of the difficulties of individualising the algorithms and how they change with the changing situation in the hospitalised patient, this technology remains some way from routine clinical use.

Implications for practice

It has become increasingly apparent from the success of enhanced recovery partnership programmes that better outcomes are achieved by having a patient pathway that commences at primary care referral. This pathway is summarised in Figure 1. Management of the surgical patient with diabetes is no different. For the reasons stated, at the time of initial referral, the diabetes and other co-morbidities should have been optimised where it is safe to do so. The referral letter to the surgical team should detail all relevant pathology and medication as well as the current HbA1c. Currently, this is poorly done [11]. If the diabetes is not optimally managed at the time of referral, advice from the diabetes team should be sought as soon as possible, to facilitate optimisation. Optimisation generally takes about three months. Identifying poorly controlled or undiagnosed diabetes at a pre-operative clinic just before elective surgery, especially if the referral was made several weeks or months previously, should no longer be acceptable.

Patients should be advised on how to manage their diabetes to facilitate day of surgery admission, and day surgery is recommended if the surgery is appropriate. Diabetes is no longer a contraindication to day surgery. Day surgery provides less time for iatrogenic complications and thus is an integral part of NHS England’s ‘Choosing Wisely’ and ‘Getting it Right First Time’ initiatives [67,68].

Summary

Peri-operative hyperglycaemia, whether the cause is known diabetes, undiagnosed diabetes or stress hyperglycaemia, is a risk factor for harm, increased length of stay and death. There is increasing evidence that peri-operative hyperglycaemia is a modifiable risk factor, and many of the interventions required to improve the outcome of surgery must be instituted prior to the actual surgical admission. These interventions depend on the multidisciplinary team communicating with each other along each stage of the patient journey and working collaboratively for the benefit of the patient and ensuring that integration of care occurs across the whole of the patient centred care pathway.

Competing interests

No competing interests declared.

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Legends to Tables and Figure

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

Table 2 The WHO and American Diabetes Association diagnostic criteria for the different types of dysglycaemia [3].

Table 3 Proposal for who should be screened for diabetes prior to referral for surgery.

Table 4 Summary of the various strategies available for peri-operative glycaemic control.

Figure 1 Comprehensive care pathway of the elective surgical patient with diabetes.

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

- Patients with undiagnosed diabetes
- Failure to recognise that the surgical patient has diabetes with resultant additional requirements
- Lack of institutional guidelines for management of diabetes
- Lack of knowledge of diabetes and its management on the part of medical and nursing staff
- Hypoglycaemia and subsequent neuroglycopaenia
- Multiple co-morbidities including microvascular and macrovascular complications e.g. coronary heart disease; renovascular disease; cerebrovascular disease; and peripheral vascular disease.
- Associated obesity in patients with type 2 diabetes
- Complex polypharmacy for the treatment of the diabetes, including misuse of insulin
- Complex polypharmacy for the treatment of the co-existing morbidity
- Inappropriate use of intravenous insulin
- Electrolyte and fluid disturbances associated with the use of intravenous insulin and the coupled fluids
- Management errors when converting from usual medication to intravenous insulin and back to usual medication
- Hyperglycaemia resulting in peri-operative infection (surgical site or systemic e.g. lower respiratory tract infection, urinary tract infection)
- Hyperglycaemia resulting in systemic complications e.g. acute coronary syndromes; acute kidney injury; and cerebrovascular events
- Hospital-acquired diabetic ketoacidosis

Table 2 The WHO and ADA diagnostic criteria for the different types of dysglycaemia [3].

	Diabetes	**'Prediabetes'**		
		HbA1c diagnosed prediabetes	**Impaired fasting glucose**	**Impaired glucose tolerance**
HbA1c criteria. IFCC units (DCCT %)	≥48 mmol.mol^{-1} (≥to 6.5%) **or**	≥43 - ≤47 mmol.mol^{-1} (6.0-6.4%)		
Random glucose	>11.1 mmol.l^{-1} **or**			
Fasting plasma glucose	≥7.0 mmol.l^{-1} **or**		6.1 - 6.9 mmol.l^{-1}	<7.0 mmol.l^{-1} **and**
Two-hour plasma glucose following a 75g oral glucose load	≥11.1 mmol.l^{-1}			≥7.8 - <11.1 mmol.l^{-1}

* These criteria are included in the term 'pre-diabetes'. IFCC, International Federation of Clinical Chemistry; WHO, World Health Organisation; ADA, American Diabetes Association

Table 3 Proposal for who should be screened for diabetes prior to referral for surgery.

- Aged >40 years old (>30 years in people of South Asian origin)
- Family history of diabetes
- Personal history of gestational diabetes
- Personal history of hypertension
- Personal history of dyslipidaemia
- Personal history of prediabetes
- Body Mass Index (BMI) >25 $kg.m^{-2}$ (23 $kg.m^{-2}$ in those of South Asian origin)
- Those on long term glucocorticoid treatment

Table 4 Summary of the strategies available for peri-operative glycaemic control.

Strategy	Pre-requisite requirement	Advantages	Disadvantages
No changes	Diet controlled T2DM with an HbA1c<8.5%	Minimal risk of iatrogenic complications	Will not control additional stress hyperglycaemia
Modification of normal glucose lowering medication	• Adequately controlled DM with a pre-existing HbA1c <8.5% • Short starvation period (<1 missed meal) • Patient able to understand instructions on how to modify normal medicines	Simple effective	• Not suitable for prolonged starvation • Some of the drugs are contra-indicated in the peri-operative period
Initiation of basal insulin with correction dose insulin	• T2DM on oral hypoglycaemic agents T2DM on oral hypoglycaemic agents • Short starvation period (<1 missed meal)	Overcomes the concern that the product data sheets of some oral hypoglycaemic agents suggest discontinuation in the peri-operative period	• Need to be seen by a diabetes specialist to facilitate safe transfer from oral hypoglycaemic agents • All the intrinsic risks of insulin prescription and administration
Continuation of continuous subcutaneous insulin infusion (CSII)	• Normally on CSII • Short starvation period (<1 missed meal) • Patient able to understand instructions on how to modify CSII	Minimal disruption to normal diabetes management	• Lack of familiarity by staff • Pump manufactures now suggesting avoidance of use in the presence of diathermy
Variable rate intravenous insulin infusion (VRIII)	• Dedicated cannula • Ability for staff to safely establish the VRIII with associated fluid • Ability for staff to check CBG hourly • Ability for staff to establish and discontinue VRIII safely • Needs two pumps	Theoretically has the ability to achieve the best degree of glycaemic control	• Lack of hourly checking of CBG predisposes to hypoglycaemia/ hyperglycaemia. • Issues with initiation and discontinuation can predispose to DKA • Choice of substrate fluid may predispose to electrolyte imbalance. • Difficult to use in day surgery
Glucose-		Simple and relatively	• Wasteful due to need to

Insulin Potassium (GIK) infusion		safe Effective absorption as administered intravenously. Only needs 1 pump	replace whole fluid bag if CBG falls out of target zone. • Will need additional fluids to prevent electrolyte imbalance
'Sliding scale' subcutaneous insulin boluses		Simple	• Does not prevent dysglycaemia • Discredited and not recommended

CBG, capillary blood glucose; DKA, diabetic ketoacidosis; DM, diabetes mellitus; CSII, continuous subcutaneous insulin infusion; T2DM, type 2 diabetes mellitus; VRIII, variable rate intravenous insulin infusion.

Figure 1 Comprehensive care pathway of the elective surgical patient with diabetes