Strategies for managing the diabetic patient

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Diabetes mellitus is now classified as either ‘type 1’ (failure of endogenous insulin production) or ‘type 2’ (‘insulin resistance’) and can be diagnosed if fasting blood glucose is >6.1 mmol/l (110 mg/dl) on two separate occasions or there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms. The prevalence of the disease is rising and may be as great as 12–14% in western populations aged over 40 years. Diabetes is complicated by micro- and macrovascular consequences of chronically elevated blood glucose concentrations, and diabetic patients are over-represented in hospital populations, particularly among patients requiring surgical interventions. It is associated with increased perioperative mortality and morbidity. Evidence is now accumulating that intensive glycaemic monitoring and the administration of insulin infusions to achieve tight glycaemic control are associated with an improvement of both perioperative mortality and morbidity.

Key words: diabetes mellitus; blood glucose; hormones; insulin; metabolism; hyperglycaemia; anaesthesia.

Recently both the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association (ADA)\(^1\) and the World Health Organization\(^2\) have recommended that the terms ‘type 1’ and ‘type 2’ replace ‘insulin-dependent’ and ‘non-insulin-dependent’ diabetes mellitus (DM), respectively. Type 1 DM results from pancreatic β-cell destruction, leaving patients at risk of ketoacidosis in the absence of exogenous insulin, while the more prevalent form of diabetes, type 2,
follows from defective insulin secretion and tissue insulin resistance. The new classification is based on aetiology rather than treatment and may encourage the use of insulin infusions in the perioperative management of patients previously described as having non-insulin-dependent DM.

In the revised definitions, the diagnosis of DM for clinical purposes is made in patients with a fasting blood glucose of 6.1 mmol/l (110 mg/dl) or above—equivalent to a plasma glucose of 7.0 mmol/l (126 mg/dl)—measured on two separate occasions unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms. Additionally, within the WHO recommendations, the diagnosis of DM can be made if a blood glucose of >10 mmol/l (plasma glucose 11.1 mmol/l) is measured on any occasion or, more specifically, 2 hours after a glucose load (75 g oral glucose). The WHO and the ADA guidelines create a new diagnostic category where fasting glucose values are above the normal range but below the DM diagnostic threshold—blood glucose 5.6–6.1 mmol/l (100–110 mg/dl), plasma glucose 6.1–7.0 mmol/l (110–126 g/dl). Such patients are described as having ‘impaired fasting glycaemia’. The changes in definition have implications for the interpretation of epidemiological studies which use the older definitions, as it is difficult to make valid comparisons between these and newer studies which use the current criteria.

The prevalence of DM in adults and children has been rising for 30 years. The prevalence of DM in the adult US population (diagnosed and undiagnosed) using ADA criteria is estimated to be 7.8%. It may be as high as 12–14% in the population aged over 40 years and may be twice this rate in certain ethnic groups. The risk of developing DM increases with age, obesity and lack of physical activity. In addition, patients may develop glucose intolerance for a variety of other reasons including pregnancy, inherited disorders (such as defects of β-cell function), diffuse disease of exocrine pancreas (such as pancreatitis), viral infections (rubella, coxsackie B, cytomegalovirus, mumps) and following administration of certain drugs (such as glucocorticoids and adrenergic agonists).

PATHOLOGY OF DIABETES MELLITUS

Type 1 DM results from a failure of insulin secretion, while type 2 DM is characterized by insulin resistance usually associated with defective insulin secretion. The absolute lack of insulin secretion in type 1 DM results in lipolysis, proteolysis and ketogenesis. These metabolic processes are inhibited by minimal levels of insulin secretion and hence are rare in type 2 DM, unless there are other physiological stresses such as sepsis or dehydration. Both type 1 and type 2 DM patients are subject to the adverse effects of hyperglycaemia. The acute problems of untreated DM include dehydration (due to the osmotic diuretic effect of glycosuria), acidaemia (due to the accumulation of ketoacids as well as lactate), weight loss, fatigue and muscle wasting (due to lipolysis and proteolysis).

The metabolic stress induced by surgery, critical illness or trauma is characterized by an increase in the secretion of catabolic hormones in the presence of a relative insulin deficiency. Hyperglycaemia arises, even in non-diabetic patients, from a combination of reduced insulin secretion and tissue insulin resistance. Intraoperative insulin infusions have been shown to reverse some of the metabolic effects of the suppression of insulin secretion, and the perioperative administration of both oral and intravenous glucose enhances postoperative glucose utilization rates. Alpha blocking agents,
such as phentolamine, can inhibit the suppression of insulin secretion following surgical stress, but such agents are not commonly used in normal clinical practice.

Diabetic patients are at an increased risk of myocardial ischaemia, cerebral infarction and renal ischaemia because of their increased incidence of coronary artery disease, arterial atheroma, and renal parenchymal disease. Long-term intensive control of blood glucose has been shown to decrease the risk of microvascular complications (including proliferative retinopathy and diabetic nephropathy) in type 1 DM and in type 2 DM. Unfortunately, large trials have not shown any reduction in the incidence of macrovascular disease (such as atherosclerotic diseases), diabetes-related mortality or all-cause mortality with intensive blood glucose control. However, tight control of blood pressure (with an angiotensin converting enzyme (ACE) inhibitor or a β-blocker) aiming for a blood pressure of <150/85 mmHg in patients with both type 2 DM and hypertension reduces the risk of diabetes-related death by 32% (including deaths secondary to macrovascular complications) and other DM-related complications by 34%.

GENERAL DIABETIC MANAGEMENT

In general, type 1 DM patients always require exogenous insulin while type 2 DM patients may require insulin but, in many cases, achieve reasonable glycaemic control with an appropriate diet and/or oral hypoglycaemic drugs. Reductions in the incidence of complications from diabetes seen in patients who achieve tight glycaemic control appear to be related to the blood glucose concentrations obtained rather than the means by which it is effected. Indeed, in overweight type 2 diabetics, metformin may be the first-line treatment of choice as it decreases the risk of diabetes-related endpoints (such as diabetes-related death, myocardial infarction, stroke, peripheral and microvascular disease) and is associated with less weight gain and fewer hypoglycaemic attacks than with insulin and sulphonylureas.

Exogenous insulin, provided by either subcutaneous injections or insulin infusion, has two substantial deficiencies when compared with endogenous insulin production: limited responsiveness to metabolic requirements, and a reversal of the normal portal–systemic insulin concentration ratio. Insulin is secreted in response to a direct glucose effect on the pancreatic islet β-cells which is modulated by a variety of neural, endocrine and paracrine factors. It is secreted in a pulsatile manner with peak and trough differences in portal concentrations as great as 25-fold over a time period of 5–20 minutes. The difference between basal and stimulated peaks is approximately fivefold. Delivery of insulin into the systemic rather than the portal circulation (as in the normal physiological state) results in relative peripheral hyperinsulinaemia.

Additionally, failure of normal insulin secretion or resistance to its effects is associated with, and evokes, a more complex hormonal state than mere insulin deficiency. Type 1 DM is characterized by the failure of secretion of the two β-cell hormones, amylin and C-peptide (secreted with insulin as part of a longer polypeptide, proinsulin), as well as insulin. Amylin is also involved in glycaemic homeostasis (by influencing gut absorption of nutrients and the regulation of glucagon secretion), and replacement therapy with the amylin analogue pramlintide may improve glycaemic control in type 1 DM patients. C-peptide has been shown in type 1 DM patients to reduce glomerular hyperfiltration and improve metabolic control, but further studies are required to define a role for C-peptide administration.

Insulin replacement therapy for diabetics must attempt to mimic two temporal patterns of endogenous insulin secretion: that of low-concentration, basal secretion...
and brief, postprandial peaks. Conventionally, this is provided by a combination of slowly absorbed, less soluble insulin (usually given once or twice daily) and rapidly absorbed, soluble insulin given at meal times. Continuous infusion of soluble insulin may be given as an alternative to long-acting preparations, but ketoacidosis is a risk in type 1 diabetics treated in this way in the event of pump failure, although better technology may have overcome this problem.27

Therapeutic insulin is usually extracted from pork pancreas or synthesized using recombinant DNA technology from Escherichia coli which allows large amounts of correctly folded protein to be made.28 There are small differences in the amino acid sequence of insulin between different species. However, modifying animal insulin to make human-sequence insulin does not reduce antibody induction or insulin resistance as had been expected initially.29 The recent development of short amino acid sequences which mimic the action of insulin (‘insulin analogues’) has again raised hopes of providing exogenous insulin therapy that avoids the production of antibodies leading to reduced efficacy. Insulin lispro and insulin glargine are, respectively, short- and long-acting insulin analogues which in early trials have been shown to be both safe and effective.30

Transplantation of pancreatic tissue has been successfully carried out for many years in a number of centres and may be of benefit in selected type 1 diabetic patients with end-stage renal failure requiring simultaneous renal transplantation.31 Implantation of islet cells, protected from immunological attack by semipermeable coatings, may hold promise in the future.32 The attraction of these techniques is that not only is the patient spared the inconvenience of administering exogenous insulin but a near-normal insulin secretion response may be obtained.

The oral hypoglycaemic drugs may be divided into five main groups:

1. sulphonylureas—which enhance the secretion of insulin in response to glucose and increase sensitivity to its peripheral actions.
2. meglitinides—which stimulate insulin secretion partly in a similar way to sulphonylureas but are shorter-acting and have a more rapid onset of action33.
3. biguanides—which promote glucose utilization and reduce hepatic glucose production. Generally metformin is well tolerated and is less likely to cause hypoglycaemia than sulphonylurea or insulin21,34.
4. thiazolidinediones—which reduce peripheral insulin resistance and may reduce hepatic glucose production35,36.
5. α-glucosidase inhibitors (acarbose)—which suppress the breakdown of complex carbohydrates in the gut, delaying the postprandial rise in blood glucose concentration.37

PERIOPERATIVE MANAGEMENT OF DM

DM is a common disease and, because of its associated microvascular and macrovascular complications, it is over-represented in the hospital surgical population. Despite this, good quality outcome data—whereby different management strategies can be assessed—are only now becoming available. Even so, there is very little evidence for what is appropriate for the perioperative management of type 1 diabetics, and much has to be extrapolated from data collected from predominately type 2 DM populations.

Poor perioperative glycaemic control in diabetic patients is well recognized as being associated with a higher risk of infection38 and, possibly, other complications such as
Evidence is accumulating that intensive perioperative glycaemic monitoring and the administration of insulin infusions to achieve tight glycaemic control, at least in perioperative diabetic cardiothoracic surgical patients, is associated with better outcomes in terms of mortality and morbidity. Indeed, the risk of postoperative infection in diabetic cardiac surgical patients can be related directly to perioperative blood glucose values rather than preoperative haemoglobin A1c (an indicator of longer term glycaemic control). This may be due to improved white cell function in diabetic patients who receive continuous infusions of insulin and glucose. Both diabetic and non-diabetic patients have been shown to benefit from very tight glycaemic control in this context (4.5–6.1 mmol/l; 80–110 g/dl).

Recommendations for the management of both type 1 and type 2 DM patients who are to undergo elective cardiac surgery are, therefore, relatively straightforward. The difficulty arises with the management of diabetic patients presenting for other surgery, especially more minor procedures where the interruption of normal nutrition and treatment may present a greater metabolic challenge than the procedure itself. The perioperative problems posed by surgery in the diabetic patient are:

1. Surgical induction of the stress response. The secretion of catecholamines, cortisol and growth hormone oppose glucose homeostasis as these hormones have ‘anti-insulin’ and hyperglycaemic effects. Glycogenolysis and gluconeogenesis are stimulated and peripheral glucose uptake is decreased.
2. Interruption of oral intake, which may be further prolonged after gastrointestinal surgery.
3. Altered consciousness masking the symptoms and signs of hypoglycaemia.
4. Circulatory disturbance associated with anaesthesia and surgery which may alter the absorption of subcutaneous insulin.

It is not practical in most current practices to admit diabetic patients several days before surgery to stabilize their anti-hyperglycaemic therapy. Admission on the day of surgery for even major procedures is common and, fortunately, seems feasible and safe. Day-case surgery and anaesthesia are provided for an increasing variety of procedures and, although many centres exclude diabetic patients, there is little evidence to support diabetes alone as a contraindication. Cataract surgery, performed under local anaesthetic block, poses very little metabolic challenge to type 2 diabetic patients. Routine perioperative starvation is by no means routinely practised, and a policy of maintaining usual medication and normal oral intake for cataract procedures is remarkably safe. A similar approach may be reasonable for supervised diabetic patients who are attending day surgical centres for minor procedures, where normal oral intake and absorption are re-established before discharge, normal medication is resumed, and adequate glycaemic monitoring is available. However, outcome data are lacking, and postoperative gastric stasis, reduced absorption of oral medications and food, or altered cutaneous perfusion in patients receiving insulin may pose an unacceptable risk to diabetics, particularly those with unknown autonomic neuropathy.

Type 2 diabetics who continue oral hypoglycaemic medication during critical illness or around the time of major surgery may be at risk of more serious complications. Biguanide therapy in type 2 DM is reported to precipitate lactic acidosis which may be fatal. It is apparently more likely in the elderly and in association with renal failure, hepatic failure, and after surgery. Metformin should be withdrawn before elective surgery and insulin therapy instigated if required, while patients receiving metformin...
who present for emergency surgery will require intense metabolic monitoring and management.

The potassium channel-blocking effect of sulphonylureas may interfere with myocardial ischaemic preconditioning. In patients undergoing angioplasty, those receiving sulphonylureas have greater mortality and morbidity than those receiving insulin. Further studies of this effect are required but, until such data are available, it is reasonable to recommend that patients taking sulphonylureas be converted to insulin several days before cardiac or other major surgery, or before procedures during which myocardial perfusion may be compromised.

Anaesthetists are maintaining tighter perioperative glucose control in recent years than they were a decade ago, and are more inclined to use insulin infusions in the management of diabetic patients. Continuous intravenous insulin infusions are a better option for glycaemic control than intermittent subcutaneous regimens, and have been demonstrated to achieve better glycaemic control and improved outcome in cardiac patients. Intermittent intravenous bolus regimens for insulin have their proponents and are not associated with gross metabolic upset. However, the advent of reliable syringe pumps and bedside testing make this very unphysiological technique difficult to defend. It is important to monitor serum potassium concentrations regularly when insulin infusions are used, and replacement may be necessary even though urinary excretion may be reduced.

During the perioperative period DM patients generally have increased insulin requirements, but the exact needs of each patient for insulin and glucose are unpredictable. Concurrently running separate infusions of glucose and insulin or an infusion of glucose mixed with insulin (with or without added potassium) can provide a safe and stable method of glycaemic control for diabetic surgical patients who are temporarily unable to be fed enterally, provided that adequate monitoring of blood glucose is carried out. Combined glucose, insulin and potassium solutions (the so-called ‘GIK’ solutions) have been advocated for many years and have the advantage of inherent safety, but separate infusions may provide better control and were more acceptable to nursing staff in one study.

Safe perioperative tight glycaemic control requires frequent, rapid and accurate blood glucose measurement. The cost and ease of use of ‘bedside’ or ‘point of care’ systems, which allow anaesthetists to obtain almost instantaneous blood glucose measurements, have improved considerably in recent years. Some systems are more accurate than others, and the site of blood sampling or the state of the peripheral circulation may affect the result. For practical perioperative management of blood glucose, a measurement system should be chosen which is accurate and consistent, is subject to quality control and is simple to use. The operator should be trained in its use and aware of potential for error. A consistent sample site should be chosen, preferably, capillary or arterial samples taken so that contamination of venous samples by infused solutions can be avoided.

Although intravenous infusions are the preferred method for the perioperative administration of insulin, it is not clear what level of glycaemic control is associated with the best risk–benefit ratio for diabetic patients, or what protocol for blood glucose measurements and infusion rates should be followed. A study of 1548 critical care patients by van den Berghe demonstrated an improved outcome in patients who had their blood glucose maintained between 4.4 and 6.1 mmol/l (80–110 g/l) compared with those in whom insulin therapy was only instigated if the blood glucose rose above 12 mmol/l (215 g/l). This beneficial effect was seen in diabetics and non-diabetics alike. The authors of a more recent observational study of 523 patients (16.4% diabetic),
in a similarly predominantly postoperative cardiothoracic surgical critical care unit, suggest a more liberal blood glucose target of \(< 8.0 \text{ mmol/l (145 g/l)}\) and, again, a beneficial effect was seen equally in diabetic and non-diabetic patients.68

Both the above studies delivered insulin by continuous infusion. In the first, insulin was prescribed according to a complex algorithm supervised by a separate nursing team (van den Berghe, personal communication). In the second, there was no specific protocol.68 No information is given in either study report about the method or quality of intraoperative glycaemic management. Traditionally, insulin is prescribed to perioperative diabetic patients according to a 'sliding scale' regimen. However, its use in the management of diabetic medical inpatients has been criticized69, and the application of nomograms with blood glucose targets is more logical and more likely to achieve control in the perioperative setting.70

Few data exist on the duration of intensive glycaemic management of diabetic patients that is associated with benefit. The management of patients in van den Berghe's study43 reverted to 'conventional management' on discharge from the intensive care unit where blood glucose concentrations were maintained at values between 10.1 and 11.2 mmol/l (180–200 g/l). A smooth transition to preoperative diabetic treatment regimens may be thwarted by factors such as a continuation of the 'anti-insulin' effect of hormones secreted as part of the stress response to surgery, persistent alterations in nutritional intake and the administration of drugs which may either reduce residual endogenous insulin secretion (in type 2 DM) or reduce insulin sensitivity. Further studies in this area are required, but a reasonable approach would be to maintain an appropriate intensity of monitoring and intervention. Clearly, re-establishing preoperative therapy without frequently monitoring its effect on blood glucose in critically ill diabetic patients or those recovering from major surgery is inappropriate. The re-establishment of normal meals after a period of continuous intravenous glucose administration or enteral feeding may also be expected to be associated with a period of poor glycaemic control and may necessitate an increased intensity of blood glucose monitoring.

ANAESTHETIC TECHNIQUE FOR DM PATIENTS

The choice of anaesthetic technique for the diabetic patient is important and should be carefully considered. The increases in circulating glucose, epinephrine and cortisol concentrations as a result of the 'stress response' to surgery in non-diabetic patients under general anaesthesia are blocked by epidural anaesthesia to the levels of T4-S5 for pelvic surgery.71–74 Further advantages of regional techniques include an awake patient who can report hypoglycaemic symptoms together with the usual advantages of excellent analgesia and less nausea/vomiting, so allowing earlier resumption of oral intake (and maybe a reduction in duration of preoperative starvation in certain patients). In one study DM patients undergoing cataract surgery took twice as long to return to eating and drinking following general anaesthesia compared to local blockade.46

Regional techniques are less good at abolishing the metabolic and hormonal responses to upper abdominal surgery, possible due to the persistence of afferent vagal activity.75 Differences may exist for type 1 and type 2 DM patients as, while epidural or spinal anaesthesia reduces the catecholamine response to surgery and the consequent hyperglycaemia, these techniques also reduce the secretion of insulin from the pancreas in response to a glucose stimulus.76 Base-line adrenergic activity appears to be
important for the normal functioning of pancreatic islet function, and this may have
important consequences in type 2 patients who still have some residual pancreatic
function.

Regional anaesthesia also avoids the potential problems of tracheal intubation.
The diabetic patient is liable to difficult laryngoscopy and intubation due to
glycosylation of the joints which results in limited mobility in one-third of patients
with long-standing DM. Preoperative detection is possible by testing for the
ability to oppose the palms and fingers. DM patients with stiff joints are unable to
do this—a positive ‘prayer’ sign.

Delayed gastric emptying due to diabetic autonomic neuropathy is found in up to
50% of type 1 DM patients and increases their risk of regurgitation and aspiration.
Preliminary studies have demonstrated that the administration of oral erythromycin
preoperatively will encourage gastric motility by stimulating motilin secretion and
lowers the risk of aspiration of stomach contents in DM patients. However, other
motility stimulants, such as cisapride, had no effect on gastric emptying in diabetics.

Of particular importance to the anaesthetist is autonomic dysfunction which is
detectable in up to 40% of type 1 and 17% of type 2 diabetics. Detection of autonomic
neuropathy in patients without symptoms has relied on assessment of heart rate
variability (HRV) and in diabetic autonomic neuropathy there is loss of HRV which
may be a contributory risk factor for ventricular arrhythmias and sudden death in these
patients. The presence of autonomic dysfunction is not automatically associated with
haemodynamic instability, and when diabetics undergoing coronary artery surgery have
been studied they demonstrated very similar cardiovascular responses to those
measured in non-diabetics.

The choice of anaesthetic drugs for general anaesthetic techniques may influence
outcome in diabetic patients. The induction agent etomidate blocks adrenal
steroidogenesis by inhibiting 11β-hydroxylase, thereby reducing cortisol synthesis.
This has been shown to reduce the hyperglycaemic response to surgery in non-diabetic
patients by 1 mmol/l, but the effect of etomidate on postoperative blood glucose in
diabetic patients has not been established.

Benzodiazepines in high doses reduce the secretion of adrenocorticotropic
hormone (ACTH) and so decrease the production of cortisol. They also dampen
sympathetic responses but increase growth hormone secretion and so result in a
decreased glycaemic response to surgery. These effects are only likely to be
relevant with continuous intravenous infusions of such drugs in intensive care
patients.

Anaesthetic techniques that use high-dose opiates have the advantage of
haemodynamic, hormonal and metabolic stability, probably by a direct effect on the
hypothalamus and higher centres to produce a blockade of the entire sympathetic
nervous system and hypothalamic—pituitary axis. In normal patients this effect will
abolish the postoperative hyperglycaemia and, therefore, may be of benefit in diabetic
patients, but this has not been fully evaluated.

The volatile anaesthetic agents halothane, enflurane and isoflurane have been shown
in vitro to inhibit the insulin response to glucose in a dose-dependent and reversible
manner, but their effects in vivo in DM patients have not been fully evaluated. Of the
newer volatile agents, sevoflurane has been shown in a pig model to have a rapid and
reversible inhibitory effect on basal and glucose-stimulated insulin secretion in a manner
similar to that of other inhalational anaesthetic agents.
SUMMARY

The prevalence of DM is rising, and so the provision of safe anaesthesia in this group of patients will become increasingly important. Type 1 DM always requires the administration of insulin, while type 2 DM may be managed with diet and/or oral hypoglycaemic drugs. Type 2 DM patients generally require conversion to an insulin regimen during times of stress, such as that associated with surgery, to maintain good glycaemic control. Good glycaemic control is particularly important in the perioperative period when poor control is associated with a higher risk of infection. Much work has been done on cardiothoracic surgical patients in whom tight glucose control (4.4–6.1 mmol/l) has been shown to improve outcome in both DM and non-diabetic patients. Continuous insulin infusions have been shown to provide better blood glucose control than intermittent subcutaneous regimens, and combined glucose, insulin and potassium solutions (GIK solutions) are inherently safe. Regional anaesthetic techniques are associated with advantages such as an awake patient who can report hypoglycaemic symptoms, excellent analgesia, and less nausea/vomiting, and such techniques avoid the potential problems of tracheal intubation. Autonomic neuropathy is detectable in 40–50% of DM patients, and this will increase the risk of regurgitation/aspiration and may be a contributory risk factor for ventricular arrhythmias and sudden death in these patients.

Practice points
- DM patients are at an increased risk of myocardial ischaemia, cerebral infarction and renal ischaemia
- poor perioperative glycaemic control is associated with a higher risk of infection in DM patients
- intensive perioperative glucose control in cardiothoracic surgical patients is associated with improved morbidity and mortality
- conversion of type 2 DM patients on sulphonylureas and metformin to insulin therapy perioperatively is recommended
- intravenous insulin infusions are the preferred method of perioperative insulin administration

Research agenda
- what duration of tight glycaemic control is associated with improved outcome in cardiothoracic surgical patients, and does this apply to other surgical groups?
- can anaesthetic techniques (high-dose opioid, etomidate, clonidine, etc.) attenuate postoperative hyperglycaemia in DM patients?
- what effects do volatile anaesthetic agents have on the insulin response to glucose in type 2 DM patients?

REFERENCES


