Anaesthetic management of patients with diabetes mellitus

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The prevalence of diabetes mellitus in both adults and children has been steadily rising throughout the world for the past 20–30 yr.³⁹ ⁵⁵ ⁹⁷ Recent changes in diagnostic criteria, if widely adopted, will probably also lead to more patients being classified as having diabetes.¹⁶ Inevitably, diabetic patients presenting for incidential surgery, or surgery related to their disease, will place an increasing burden on anaesthetic services. Conflict will occur between an economic need to minimize hospital stay and traditional approaches to managing perioperative diabetic patients that rely on a period of inpatient preoperative ‘stabilization’. Better glycaemic control in diabetic patients undergoing major surgery has been shown to improve perioperative mortality and morbidity.⁴⁴ ⁹⁹ Simple avoidance of hypoglycaemia and gross hyperglycaemia are no longer adequate in the light of this knowledge. While there can be little argument about the management of diabetic patients undergoing major procedures, their management for minor surgery is an increasing dilemma. Under what circumstances are day-case anaesthesia and surgery appropriate? Does admission on the day of surgery add to the risk for the diabetic patient? What investigations, if any, are needed to assess the cardiovascular system of an asymptomatic diabetic who presents for major surgery? Unfortunately, there are few data to provide answers to these questions. An understanding of the pathophysiology of diabetes and of the importance of recent research should improve the perioperative care of diabetic surgical patients. This review will discuss some recent developments in the field. It will not provide ‘recipes’ or algorithms for management. These can be found in any of the standard texts.

Revised diagnostic criteria for diabetes mellitus

Recently, both the American Diabetes Association (ADA) and the World Health Organization (WHO) published recommendations for new diagnostic criteria for diabetes mellitus.¹ ¹⁰⁶ Both bodies advise a reduction in the threshold limit for fasting plasma glucose concentrations and reaffirm a more aetiological based nomenclature. The terms type 1 (pancreatic B-cell destruction) and type 2 (defective insulin secretion and, usually, insulin resistance) diabetes are recommended to replace completely the frequently misleading terms ‘insulin-dependent’ and ‘non-insulin-dependent’ diabetes. The ADA has specified that the diagnosis of diabetes mellitus should be made if a ‘casual’ (random) plasma glucose value in an asymptomatic individual is >11.1 mmol litre⁻¹.¹ If a fasting plasma glucose is >7.0 mmol litre⁻¹ (6.1 mmol litre⁻¹ blood glucose) in an asymptomatic individual, the test should be repeated on a different day and a diagnosis made if the value remains above this limit. The ADA defines fasting plasma glucose concentrations between 6.1 and 7.0 mmol litre⁻¹ (5.6–6.1 mmol litre⁻¹ blood glucose) as representing ‘impaired fasting glycaemia’. The WHO also recommends that a diagnosis of diabetes mellitus be made if a random plasma glucose concentration is >11.1 mmol litre⁻¹ (venous whole blood >10.0 mmol litre⁻¹). It can also be diagnosed with a fasting plasma glucose concentration of >7.0 mmol litre⁻¹ and a second similar test or an oral glucose tolerance test producing a result in the diabetic range.

The change in the fasting plasma glucose concentrations used to define diabetes and the role of a standard oral glucose tolerance test may make it difficult to compare epidemiological studies using these new criteria with those using previous ones. Inevitably, some individuals will be diagnosed as having diabetes using criteria based solely on (lower) fasting plasma glucose concentrations who would not have been so diagnosed under the earlier definitions. There will be others who would have fulfilled the definition using an oral glucose tolerance test but who will have acceptable fasting values. Thus it is likely that the new definitions will
define as diabetic a group of glucose intolerant individuals.\textsuperscript{52}

In addition to the two common types of diabetes, a number of causes of glucose intolerance can be defined according to a specific causal or pathological process. Gestational diabetes is glucose intolerance which has its onset in, or is first diagnosed during, pregnancy. The severity varies and the definition applies whether or not insulin is administered in treatment. Women with diabetes diagnosed before pregnancy are defined as having ‘diabetes mellitus and pregnancy’, not gestational diabetes.\textsuperscript{1} The neonatal outcome of type 1 diabetic women who become pregnant is poor. Their infants are approximately five times more likely to be stillborn and 10 times more likely to have congenital malformations than those born to non-diabetic mothers.\textsuperscript{10} Management in a specialist centre may improve the incidence of perinatal mortality.\textsuperscript{34} Abnormally increased membrane transport of glucose, even in mothers whose diabetes is well controlled, may explain the continuing high rates of congenital malformations (particularly macrosomia) despite improved treatment.\textsuperscript{48} Increasing the frequency of insulin administration from two to four times daily during pregnancy can lead to better maternal glycaemic control with a lower incidence of neonatal hypoglycaemia and hyperbilirubinaemia without increasing the risk of maternal hypoglycaemia.\textsuperscript{73}

There is a number of rare genetic causes of glucose intolerance. Among these are defects of B-cell function (formerly called maturity-onset diabetes of the young, or MODY) and defects in insulin action (formerly called type A insulin resistance). Diffuse diseases of the exocrine pancreas (such as pancreatitis), specific viral infections which destroy pancreatic B cells (rubella, Coxsackie B, cytomegalovirus, mumps and others) and immune-mediated processes (insulin autoantibodies or insulin receptor antibodies) can also lead to a ‘diabetic state’.\textsuperscript{1} Endocrinopathies associated with excess secretion of counter-regulatory hormones (such as growth hormone, cortisol, glucagon and epinephrine) can lead to hyperglycaemia.

A number of drugs can induce glucose intolerance either by inhibiting the secretion of insulin or by interfering with the peripheral action of insulin.\textsuperscript{1} In anaesthesia, glucocorticoids and adrenergic agonists are most frequently implicated. The new oral corticosteroid, dexamethasone, may be less ‘diabetogenic’ than prednisolone or betamethasone.\textsuperscript{2}

‘Metabolic syndrome’ (also called syndrome X or insulin resistance syndrome) is a non-causally linked cluster of symptoms which carry a high risk of macrovascular disease. The cluster includes impaired glucose tolerance or diabetes, insulin resistance, raised arterial pressure, raised plasma triglycerides, central obesity and microalbuminuria.\textsuperscript{1}

**Pathophysiology**

Type 1 diabetics completely lack insulin secretion, making them prone to lipolysis, proteolysis and ketogenesis. These processes are inhibited by minimal levels of insulin secretion and are rare in type 2 diabetics unless there is an additional stress such as sepsis or dehydration.\textsuperscript{122} Obviously, both groups are subject to the effects of hyperglycaemia.

Diabetics are at increased risk of myocardial ischaemia, cerebrovascular infarction and renal ischaemia because of their increased incidence of coronary artery disease,\textsuperscript{64} arterial atheroma\textsuperscript{51} and renal parenchymal disease.\textsuperscript{14} Increased mortality is found in all diabetics undergoing surgery\textsuperscript{44 90} and type 1 diabetics are particularly at risk of post-operative complications.\textsuperscript{111} Increased wound complications are associated with diabetes,\textsuperscript{24 64 72 126} and anastomotic healing is severely impaired when glycaemic control is poor.\textsuperscript{118}

The ‘stress response’ to surgery is associated with hyperglycaemia in non-diabetic patients as a result of increased secretion of catabolic hormones in the presence of a relative insulin deficiency. This deficiency arises from a combination of reduced insulin secretion\textsuperscript{61} and insulin resistance.\textsuperscript{109} Insulin resistance may result, in part, from the increase in secretion of catecholamines, cortisol and growth hormone\textsuperscript{42} and involves an alteration of post-receptor binding of insulin and subsequent reduction of transmembrane glucose transport.\textsuperscript{79} Some, at least, of the metabolic effects of the suppression of insulin secretion are reversed by intraoperative insulin infusion\textsuperscript{37} and both oral and i.v. perioperative administration of glucose enhance postoperative glucose utilization rates.\textsuperscript{56 62 80}

**Adverse effects of hyperglycaemia**

The consequences of a reduction in, or complete lack of, insulin-mediated metabolic processes can be classified according to chronicity and to histopathological effects.

Acute consequences of untreated, or inadequately treated, diabetes mellitus include dehydration (resulting from the osmotic diuretic effect of glycosuria), acidosis (because of accumulation of lactic and/or keto acids), fatigue, weight loss and muscle wasting (because of lipolysis and proteolysis in absolute insulin deficiency). Ketoacidosis is rare in type 2 diabetics but is frequently a presenting symptom of type 1 disease. It is a medical emergency that still carries a considerable mortality rate of up to 15%.\textsuperscript{4 49} The mortality of hyperosmolar non-ketotic hyperglycaemic coma in type 2 diabetics may be even greater,\textsuperscript{65} probably reflecting a more elderly population with a higher incidence of co-existing disease.

Ketoacidosis is treated by rehydration and insulin infusion with frequent measurements of serum electrolytes and acid-base status. Sequential estimations of blood β-hydroxybutyrate concentrations and concomitant continuation of intensive insulin therapy may expedite treatment.\textsuperscript{124} Non-ketotic hyperglycaemic coma is frequently precipitated by infection and is commonly associated with
multi-organ system dysfunction. Blood glucose concentrations may be extremely high.\textsuperscript{33}

Chronic effects of diabetes can be divided into microvascular (including proliferative retinopathy and diabetic nephropathy), neuropathic (autonomic and peripheral neuropathies) and macrovascular complications (atherosclerotic disease). The incidence of microvascular and neuropathic complications in types 1 and 2 diabetes is similar when adjusted for duration of disease and quality of glycaemic control. The cumulative lifetime incidence of proliferative retinopathy, proteinuria and distal neuropathy is roughly 50\% for both type 1 and type 2 diabetes. This implies that the primary cause of these complications is hyperglycaemia itself, as the underlying metabolic pathology is different for type 1 and type 2 disease.\textsuperscript{31} Macrovascular complications (as measured by rates of coronary artery, cerebrovascular and peripheral vascular disease) are also similar for type 1 and 2 diabetes (cardiovascular mortality is 30–54\% for type 1 and 38–41\% for type 2 diabetes).\textsuperscript{31} In type 2 patients, at least, abnormally high concentrations of plasminogen activator inhibitor-1 (PAI-1) and, therefore, impaired fibrinolysis, have been implicated in the accelerated rates of development of atherosclerotic disease.\textsuperscript{83}

Improved glycaemic control has a beneficial effect on microvascular and neuropathic complications in type 2 diabetes.\textsuperscript{114} Although there is probably no adverse effect,\textsuperscript{83} improvement in glycaemic control alone appears not to improve the incidence of macrovascular disease in these patients.\textsuperscript{114} However, tight control of blood pressure (with an angiotensin-converting enzyme inhibitor or a \(\beta\)-blocker) in patients with type 2 diabetes and hypertension reduces the risk of diabetes-related death, including that secondary to macrovascular complications, as well as the risk of other diabetes-related complications and eye disease.\textsuperscript{115,116}

**Diabetic therapy**

**The problems of insulin replacement**

Insulin is secreted into the bloodstream from pancreatic B cells via the portal system so that there is normally a portal–peripheral insulin concentration gradient which cannot be mimicked by subcutaneous or i.v. insulin administration. Additionally, even the most sophisticated artificial insulin delivery systems cannot hope to replicate the complex local interaction between the B cells and A, D and PP cells of the islets of Langerhans (which secrete glucagon, somatostatin and pancreatic polypeptide, respectively) and the effects of the extrapancreatic neurohumoral system. Insulin secretion in response to varying states of feeding or starvation changes by 20- to 50-fold and maintains a basal insulin secretion during the fasting state. Insulin administered subcutaneously, even if timed optimally, will inevitably have inadequate peak concentrations for expected postprandial periods, and its duration of action may be frequently too short to avoid periods of hypoinsulinaemia and subsequent risk of lipolysis and proteolysis in patients with no endogenous insulin secretion.

Insulin is synthesized in the pancreas as part of a longer-chain protein called proinsulin. This is cleaved by membrane-bound proteases producing the polypeptides insulin and C-peptide. These two polypeptides are secreted into the circulation in equimolar amounts. C-peptide is useful experimentally in determining native insulin production in type 2 diabetic subjects receiving insulin. It was once thought that C-peptide had no physiological role other than facilitating the folding of the proinsulin molecule. However, more recent studies point to a possible role for C-peptide in glucose transport in skeletal muscle, renal tubular function and in the prevention of autonomic neuropathy.\textsuperscript{119}

**Hypoglycaemic therapy**

Type 1 diabetics require insulin. Type 2 diabetics may require insulin but, in many cases, maintain reasonable glycaemic control with an appropriate diet and often the use of oral hypoglycaemic drugs.

Therapeutic insulin may be extracted from beef (now rarely used) or pork pancreas, or synthesized using recombinant DNA technology from *Escherichia coli*.\textsuperscript{6} The amino acid sequences of insulin differ somewhat between species; however, modifying porcine insulin can produce human-sequence insulin. It was hoped that the replacement of animal- by human-sequence insulins would reduce the induction of antibodies and therefore insulin resistance, but clinical trials have been disappointing.\textsuperscript{56}

The three types of insulin preparation are classified according to their length of action. Soluble insulins have a rapid onset and short duration of action (depending upon the route of administration). When injected subcutaneously the duration of action is from 30 min up to 8 h with a peak at 2–4 h. Human-sequence soluble insulin has a slightly shorter onset time and duration of action. Insulin lispro, a recently introduced recombinant human insulin analogue, has an even shorter duration of action. Soluble insulin injected i.v. has a half-life of approximately 5 min.\textsuperscript{6}

Longer-acting insulin preparations are made with suspensions of insulin with either protamine (‘insophane insulin’) or zinc (‘crystalline insulin’) salts or both together. They are often administered in combination with soluble insulin to obtain rapid onset together with a long duration of action.\textsuperscript{6} They are not suitable for i.v. use. Long-acting insulins may act for up to 36 h for animal-\textsuperscript{51} and 24 h for human-sequence preparations.\textsuperscript{57}

There are four groups of oral hypoglycaemic agents: the sulphonylureas, the biguanides, the (recently developed) thiazolidinediones and modifiers of glucose absorption from the gut. In the main, sulphonylureas enhance the secretion of insulin in response to glucose and increase sensitivity to its peripheral actions. Biguanides (metformin is the only compound in this group available in the UK) promote
glucose utilization and reduce hepatic glucose production. Thiazolidinediones, which are still under clinical evaluation (and currently under a cloud because of reported hepatotoxicity), enhance insulin action in the periphery and inhibit hepatic gluconeogenesis, perhaps via a specific receptor mechanism. The \( \alpha \)-glucosidase inhibitor, acarbose, suppresses the breakdown of complex carbohydrates in the gut and therefore delays the rise in postprandial blood glucose concentrations.\(^{100} \)

Intensive, effective glycaemic control of type 2 diabetes results in a reduction of microvascular, but probably not macrovascular, complications of the disease.\(^{83, 114} \) Where adequate control can be achieved (haemoglobin A1c concentration 7–8%\(^{31} \)) there is no clear advantage for any therapeutic agent; oral hypoglycaemics and insulin have similar effects.\(^{76} \) Metformin may be a better choice in obese type 2 diabetics. It was associated with a lower incidence of mortality and diabetes-related morbidity when used as a first-line treatment compared with either sulphonylureas or insulin in the recently reported UK Prospective Diabetes Study (UKPDS).\(^{113} \) However, addition of metformin to patients receiving sulphonylureas in the UKPDS was associated with a worrying increase in mortality. Despite concerns about rare but potentially lethal lactic acidosis, which may be more likely in the elderly,\(^{100} \) in association with renal failure\(^{25} \) and hepatic failure and after surgery,\(^{71} \) metformin is well tolerated and less likely to cause hypoglycaemia than sulphonylureas or insulin.\(^{28, 113} \)

Interest in the potassium channel-blocking effect of sulphonylureas and, hence, interference with myocardial ischaemic preconditioning, has increased recently.\(^{5} \) Glimepiride may not block potassium channels,\(^{58} \) but angioplasty patients receiving sulphonylureas have greater mortality and morbidity than those given insulin.\(^{30} \) The general implications of this observation are not clear but, until data from well-conducted studies are available, it would seem prudent to convert patients taking sulphonylureas to insulin several days before cardiac or other major surgery or procedures where myocardial perfusion may be compromised.\(^{30} \)

**Perioperative therapy**

Type 2 diabetics not receiving insulin and undergoing minor surgery usually can be managed satisfactorily without insulin.\(^{108} \) However, diabetic patients scheduled for major surgery, who are receiving hypoglycaemic medication or who have poor glycaemic control, should be established on insulin therapy preoperatively. Continuous i.v. infusion of insulin is a better option than intermittent s.c. bolus regimens\(^ {11} \) and, at least in perioperative cardiac surgical patients, may be associated with improved outcome.\(^{27} \)

Although intermittent i.v. bolus regimens are still used,\(^ {37} \) this approach is difficult to recommend.\(^ {38, 45} \)

Adsorption of insulin on to the surface of syringes, i.v. fluid bags and i.v. giving sets is an unavoidable problem. In solutions with a concentration of insulin of >400 ng ml\(^{-1} \) (≈ 10 U litre\(^{-1} \)) the effect is minimal.\(^{8} \) However, significant amounts of insulin may be adsorbed on to giving sets, particularly if they have a relatively high surface area, thereby reducing initial rates of insulin delivery if a high-volume, low-insulin concentration regimen is used.\(^{69} \) More consistent delivery can be achieved with more concentrated solutions of lower volume administered from a syringe.\(^{92} \)

When normal oral nutrition is not possible, parenteral administration of carbohydrate is required to safeguard against inadvertent hypoglycaemia and excessive catabolism. Safety is always a concern when insulin infusions are administered. Glucose–insulin–potassium (GIK) systems, such as the Alberti regimen, are inherently safe because they provide insulin and glucose in the same solution.\(^{107} \) With separate glucose and insulin infusions one may be stopped inadvertently with potentially disastrous consequences. However, separate infusions were preferred by nursing staff and resulted in marginally improved perioperative glycaemic control when compared with a GIK system in one randomized controlled trial of 58 surgical patients.\(^{101} \) Fifty per cent glucose solutions containing 0.25 or 0.5 U insulin ml\(^{-1} \) can provide amounts of glucose and insulin equivalent to the more conventional systems using 10% glucose and avoid the administration of large volumes of free water.\(^{68} \) However, the hypertonic 50% solution needs to be infused into a central vein.\(^{68} \)

**The metabolic challenge of surgery for the diabetic patient**

The immediate perioperative problems facing the diabetic patient are: (i) surgical induction of the stress response with catabolic hormone secretion; (ii) interruption of food intake, which may be prolonged following gastrointestinal procedures; (iii) altered consciousness, which masks the symptoms of hypoglycaemia and necessitates frequent blood glucose estimations; and (iv) circulatory disturbances associated with anaesthesia and surgery, which may alter the absorption of subcutaneous insulin.

Surgery evokes the ‘stress response’, that is, the secretion of catecholamines, cortisol, growth hormone and, in some cases, glucagon. These hormones oppose glucose homoeostasis, as they have ‘anti-insulin’ and hyperglycaemic effects. Gluconeogenesis is stimulated and peripheral glucose uptake decreased. Although diabetics need increased insulin during the perioperative period, requirements for glucose and insulin in this period are unpredictable and close monitoring is essential, especially in the unconscious or sedated patient.

Diabetic patients established on longer-acting insulin are at risk of hypoglycaemia if regular food intake is interrupted, and of lipolysis and proteolysis if insulin therapy is delayed. Postoperative wound healing and infection may be
influenced by the adequacy of perioperative glycaemic control.\textsuperscript{72, 118}

**Options for the perioperative management of diabetes**

The main concern for the anaesthetist in the perioperative management of diabetic patients has been the avoidance of harmful hypoglycaemia; mild hyperglycaemia has tended to be seen as acceptable. This has been attributed to the difficulties of measuring blood glucose when the reduced level of consciousness perioperatively masks signs and symptoms of hypoglycaemia. However, in the past decade the availability of more accurate and easy-to-use glucose monitors, with evidence that good glycaemic control improves short-term outcome, makes the practice of ‘permissive hyperglycaemia’ unacceptable.

One survey of anaesthetic practice in the Oxford region of the UK suggests that anaesthetists are likely to manage hyperglycaemia in perioperative diabetic patients more aggressively now than they did in 1985.\textsuperscript{22} However, of the 172 respondents in this survey, 22% still preferred to maintain blood glucose at >10 mmol litre\textsuperscript{-1} in diabetic patients and 2% preferred a value of >13 mmol litre\textsuperscript{-1}. The vast majority of respondents maintained glycaemic control for type 1 diabetic patients undergoing major surgery with glucose and insulin infusions, either separately or combined. Nearly 90% of respondents did not consider it necessary, in type 2 diabetics undergoing minor surgery, for there to be any greater intervention than omitting the usual hypoglycaemic therapy and avoidance of glucose-containing i.v. solutions. Surprisingly, 17% of senior anaesthetists had the same approach to type 2 diabetics undergoing major surgery. Cost and inconvenience may influence decisions about the intensity of blood glucose management and, until recently, there has been little evidence to support strategies aimed at tightening glycaemic control.\textsuperscript{35} Between the two extremes of a diet-controlled stable type 2 diabetic presenting for minor surgery and the ‘brittle’ type 1 patient undergoing major abdominal surgery, about whom there is little argument, there remains considerable disagreement about the ideal regimen for managing blood glucose.

**Monitoring techniques**

The advent of semi-automated devices has improved the accuracy of measurement of blood and capillary glucose concentrations in both the community and hospital.\textsuperscript{7} For these machines to be effective they must be calibrated regularly and people using them must be trained.

Recent work has suggested that measurement of circulating β-hydroxybutyrate concentrations may be helpful in treating acutely unstable diabetes\textsuperscript{70, 124} and the development of a bedside device will enable the usefulness of sequential estimations of ketonaemia to be assessed.\textsuperscript{70}

Glycosylated haemoglobin (HbA\textsubscript{1c}) measurement has no value in the perioperative period but is a valuable guide to long-term glycaemic control.\textsuperscript{31} If HbA\textsubscript{1c} values have been consistently >8% it is probable that microvascular complications of diabetes are present.

**Anaesthetic technique and the diabetic patient**

Anaesthetic techniques, particularly the use of spinal, epidural, splanchnic or other regional blockade, may modulate the secretion of the catabolic hormones and any residual insulin secretion. The perioperative increase in circulating glucose, epinephrine and cortisol concentrations found in non-diabetic patients exposed to surgical stress under general anaesthesia is blocked by epidural anaesthesia.\textsuperscript{39, 125} The perioperative infusion of phentolamine, a competitive α-adrenergic receptor blocking drug, decreases the glycaemic response to surgery by partially reversing the suppression of insulin secretion.\textsuperscript{75} Interestingly, a small study of non-diabetic patients showed preservation of the insulin response to a bolus of glucose after the use of low, but not high, spinal anaesthesia.\textsuperscript{30} This implies that basal islet cell secretion is maintained by β-adrenergic stimulation. Whether extensive spinal blockade is detrimental in type 2 diabetics is not known. Cataract surgery in type 2 patients using local analgesia, when compared with general anaesthesia, was associated with much less disruption of glucose metabolism: blood glucose, lactate, β-hydroxybutyrate, serum cortisol, insulin and plasma non-esterified fatty acid concentrations were measured peroperatively.\textsuperscript{3}

Diabetic patients undergoing surgery with neural blockade will usually resume oral intake earlier than after general anaesthesia. It is now common practice in cataract surgery to allow normal oral intake and hypoglycaemic therapy throughout the perioperative period. In a series of 12 000 cataract extractions under local anaesthesia, in which patients were not starved, eight patients showed evidence of brain stem anaesthesia, and one developed cerebral spread of local anaesthetic solution. In only one patient was surgery postponed because of persistent nausea.\textsuperscript{43} However, the possibility of having to convert a regional technique to general anaesthesia may militate against this practice in other forms of surgery. At present, there is no evidence that regional anaesthesia alone, or in combination with general anaesthesia, confers any benefit in the diabetic surgical patient, in terms of mortality and major complications.

Regional anaesthesia may carry greater risks in the diabetic patient with autonomic neuropathy. Profound hypotension may occur with deleterious consequences in a patient with co-existing coronary artery, cerebrovascular or renovascular disease. The risks of infection and vascular damage may be increased with the use of regional techniques in diabetic patients; epidural abscesses occur more commonly following spinal and epidural anaesthe-
sia. Conversely, a diabetic peripheral neuropathy presenting after epidural anaesthesia may be confused with an anaesthetic complication of regional blockade.

**Anaesthetic agents and diabetes**

Induction agents may affect glucose homeostasis perioperatively. Etomidate blocks adrenal steroidogenesis and hence cortisol synthesis, by its action on 11β-hydroxylase and cholesterol cleavage enzymes, and consequently decreases the hyperglycaemic response to surgery by approximately 1 mmol litre\(^{-1}\) in non-diabetic subjects.\(^{26}\) The effects on diabetic patients have not been established.

Benzodiazepines decrease the secretion of ACTH, and so the production of cortisol, when used in high doses during surgery.\(^{18}\) They reduce sympathetic stimulation but, paradoxically, stimulate growth hormone secretion and result in a decrease in the glycaemic response to surgery. These effects are minimal when midazolam is given in usual sedative doses, but may be relevant if the drug is given by continuous i.v. infusion to patients in intensive care.

High-dose opiate anaesthetic techniques produce not only haemodynamic, but also hormonal and metabolic stability. These techniques effectively block the entire sympathetic nervous system and the hypothalamic–pituitary axis, probably by a direct effect on the hypothalamus and higher centres.\(^{36}\) Abolition of the catabolic hormonal response to surgery will, therefore, abolish the hyperglycaemia seen in normal patients and may be of benefit in the diabetic patient.\(^{59}\)

Halothane, enflurane and isoflurane, in vitro, inhibit the insulin response to glucose in a reversible and dose-dependent manner.\(^{19}\)\(^{32}\) The effect of propofol on insulin secretion is not known. Diabetic patients show a reduced ability to clear lipids from the circulation.\(^{123}\) Although this is unlikely to be relevant during short anaesthetics when propofol is used for maintenance or as an induction agent only, it may have implications for patients receiving propofol for prolonged sedation in the intensive care unit.

**Complications of diabetes**

Microvascular, neuropathic and macrovascular complications of diabetes mellitus are of special concern for the anaesthetist. Of particular importance are coronary heart disease, diabetic nephropathy and autonomic neuropathy because these may have a direct effect on the development of perioperative complications. In addition, young patients with long-standing type 1 diabetes and poor glycaemic control were found to have significantly decreased lung volume, lung diffusing capacity and cardiac stroke index during exercise when compared with patients treated with intensive insulin therapy.\(^{78}\)

Because of glycosylation of collagen in the cervical joints, part of a generalized phenomenon called ‘stiff joint syndrome’, diabetic patients are more likely to present with difficult laryngoscopy and intubation. Stiffness of the fourth and fifth interphalangeal joints is a common feature and the resulting alteration in palm print may be a good predictor of difficult intubation.\(^{74}\) However, in one retrospective review of the anaesthetic records of 725 patients who underwent renal and/or pancreatic transplantation (of whom 209 were diabetic), none were reported as having ‘moderate to extreme difficulty’ of laryngoscopy. A total of 4.8% of the diabetics presented ‘minimal to moderate’ difficulty for intubation compared with 1.0% of the non-diabetics. All were intubated successfully although one was intubated electively with the aid of a fibre-optic flexible laryngoscope.\(^{120}\)

**Coronary heart disease**

Diabetic men are more than four times as likely, and women five times as likely, to have coronary heart disease (CHD) than non-diabetics.\(^{15}\) The annual cardiac event rate for untreated patients is 2.5% and even treated patients have more aggressive coronary disease and experience worse outcomes at any stage of the disease.\(^{96}\) Some patients may have significant CHD causing myocardial ischaemia and even suffer myocardial infarction without typical symptoms. This may result from autonomic neuropathy,\(^{67}\) but such ‘silent ischaemia’ is unlikely to occur without the coexistence of multiple risk factors. However, even selective screening targeted at patients with specific multiple risk factors has been discouraged because there is no evidence to support intervention (in the form of angioplasty or surgery) for asymptomatic diabetic patients.\(^{99}\) What is the anaesthetist to do when presented with an asymptomatic diabetic patient who has some or all of the other risk factors such as advanced age, smoking, hyperlipidaemia and hypertension? Perioperative management of such a patient may be altered if it is known that there is a likelihood of myocardial ischaemia even if intervention by coronary artery bypass grafting or angioplasty (although perhaps not coronary stenting) carries an unacceptable risk/benefit ratio.\(^{81}\) Asymptomatic type 1 diabetics with severe nephropathy scheduled for renal transplantation have been shown to benefit from preoperative screening and appropriate coronary revascularization.\(^{65}\) A similar strategy may well be appropriate for high-risk diabetics, particularly those with ‘metabolic syndrome’, about to undergo major, elective non-cardiac surgery.

Diabetic patients have a worse outcome after coronary artery bypass surgery\(^{96}\) and tend to stay in hospital longer.\(^{50}\) They are more likely to develop postoperative renal failure\(^{13}\) and suffer delayed stroke.\(^{46}\) Deep sternal wound infection rates are also higher than in the non-diabetic population,\(^{126}\) but the incidence may be reduced by improving diabetic control with continuous insulin infusions.\(^{27}\) Mortality following coronary artery bypass surgery in diabetics is generally reported as significantly greater than that in non-diabetics.\(^{110}\)
Diabetic nephropathy
In most countries, the leading causes of end-stage renal failure are hypertension and diabetes mellitus. In the USA, 30–40% of patients with type 1 diabetes will develop diabetic nephropathy and end-stage renal failure.93 There is now substantial evidence that angiotensin-converting enzyme (ACE) inhibitors have a renal protective effect in patients with type 1 diabetes.61 This may also be the case in type 2 diabetes, but the evidence is less convincing. No agent has been shown to be renoprotective in the perioperative period and some of the traditional drugs used for this purpose may be harmful.17 105 Ensuring adequate renal perfusion by expanding the extracellular space (salt loading) or, more specifically, the intravascular space with appropriate haemodynamic monitoring may reduce the risk of postoperative renal dysfunction. Hydration with 0.45% sodium chloride solution alone provides better protection against radiocrystalloid-induced renal failure in at-risk subjects than saline with the addition of furosemide or mannitol.102

Autonomic neuropathy
Diabetic patients frequently develop neuropathy, most commonly a distal symmetrical sensory or sensorimotor polyneuropathy with a variable degree of autonomic involvement.12 Autonomic dysfunction, which is of particular importance to the anaesthetist, is detectable in up to 40% of type 171 and 17% of type 2 diabetic patients.23 Only a small proportion of these patients are symptomatic, with signs and symptoms such as gastroparesis, postural hypotension, gustatory sweating, diabetic diarrhoea and bladder paresis.121 Many pathogenic mechanisms have been suggested for diabetic autonomic neuropathy, including local ischaemia,112 tissue accumulation of sorbitol,20 altered function of neuronal Na+/K+/ATPase pump activity103 and immunologically mediated damage.21

The cardiovascular effects of insulin are paradoxical in autonomic neuropathy patients. In normal subjects, i.v. or s.c. insulin administration activates the sympathetic nervous system, causing an increase in circulating norepinephrine, supine arterial pressure and peripheral vascular resistance.85 At the supraphysiological concentrations often used in the treatment of diabetes, vasodilation occurs with decreased peripheral vascular resistance and increased flow.85 These observations suggest that insulin has dual effects, namely a vasoconstrictor effect mediated by the sympathetic nervous system at low insulin concentrations, and a vasodilator effect, perhaps mediated by nitric oxide release at higher concentrations. In patients with autonomic neuropathy, insulin causes a decrease in supine arterial pressure and exacerbates postural hypotension.

Detection of autonomic neuropathy in patients without symptoms has relied on methods such as assessment of heart rate variability (HRV).104 In diabetic autonomic neuro-

pathy, there is loss of HRV. The severe impairment of HRV in patients with end-stage diabetic nephropathy probably results from autonomic neuropathy and partly from coexisting heart disease.57 The loss of HRV may be a contributory risk factor for ventricular arrhythmias and sudden death in these patients.57 The presence of autonomic dysfunction in diabetics undergoing coronary artery surgery is not, however, automatically associated with haemodynamic instability during induction and the cardiovascular responses in non-diabetic and diabetic patients were very similar.53

Diabetic gastroparesis is characterized by a delay in gastric emptying without any gastric outlet obstruction.117 The increased amount of gastric contents enhances the risk of acid aspiration during the induction of anaesthesia.82 These patients are often asymptomatic and unpredictable difficulties in tracheal intubation increase even further the risk of aspiration.88 Studies have shown little effect of prokinetic agents, such as cisapride, in reducing the volume of gastric contents in diabetics.89

Postoperative respiratory arrest seems to be more common in diabetic patients. Acute, unexpected respiratory problems in the recovery room are more common in men, in those aged >60 years, and in obese or diabetic patients.95

Wound healing and infection
It has long been recognized that wound healing is impaired in diabetic patients.9 44 This observation has been repeated in animal models where it has been shown that pre- and postoperative glycaemic control with insulin, not postoperative alone, can restore normal anastomotic healing.118 Recent work suggests that better glycaemic control with insulin infusions may reduce the incidence of deep sternal wound infections in diabetic patients who have undergone cardiac surgery.27 This observation is supported by a study demonstrating better preservation of neutrophil function with ‘aggressive’ glycaemic control using an insulin infusion, compared with intermittent therapy, in diabetic cardiac surgical patients.96 Interestingly, high-dose insulin and glucose infusions, aimed at maintaining supranormal plasma insulin concentrations and euglycaemia in non-diabetic burns patients, significantly decreased donor-site healing time after skin grafting.84

Conclusion
It is well known that diabetic patients are at greater risk of perioperative mortality and morbidity after major surgery and have a higher incidence of co-existing disease. Over recent years evidence has accumulated that improving glycaemic control in both the short and long term improves outcome. Attention to detail in the day-to-day management of the disease itself and associated conditions, such as hypertension, reduces the devastating consequences of microvascular and macrovascular complications. In add-
ition, a more aggressive approach to glycaemic control in the perioperative period results in better wound healing, lower morbidity and shorter hospital stays. Gone are the days when anaesthetists could tolerate ‘permissive hyperglycaemia’ with the idea that this approach was in the patient’s best interest. Tight metabolic control in the perioperative period is imperative and is a goal which is attainable in most patients.

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