Glucose control: What benefit, what cost?

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Introduction
Diabetes mellitus (DM) is the most common non-communicable disease worldwide. Presently there are about 150 million diabetics; it affects between 1 and 2% of the population in the United Kingdom (UK), and about 10% of the population in the United States of America (USA). There may also be an equal number of undiagnosed patients. Diabetes affects about 1 in 6 patients over the age of 65 years, and 1 in 4 over the age of 85 years; over 90% of patients are non-insulin dependent (type 2) diabetics.

The disease ‘diabetes mellitus’ has undergone a reclassification on the basis of the aetiology of the hyperglycaemia rather than therapy required: causes of hyperglycaemia therefore include insulin deficiency, insulin resistance, excessive hepatic gluconeogenesis or a combination of these. The American Diabetes Association (ADA) presently recognises four types of diabetes mellitus1:

• Type 1 – due to β-cell destruction and insulin deficiency
• Type 2 – insulin resistance; or secretory defects with or without resistance
• Specific types: genetic defects of β-cell function, diseases of exocrine pancreas, endocrinopathies, drug or chemical induced DM, infections, genetic defects associated with diabetes
• Gestational diabetes

The ADA defines diabetes on the results of a fasting glucose > 126 mg/dL (7.0 mmol/l), a random non-fasting glucose > 200 mg/dL (11.1 mmol/l), or a blood glucose > 200 mg/dL in 2 hour sample after 75 gm Glucose Tolerance Test. Normal value for fasting is < 100 mg/dL (5.6 mmol/l), impaired glucose tolerance presenting with a fasting glucose between 100 and 126 mg/dL, or a two hour post-prandial value > 140 and < 200 mg/dL.

The progression of the development of diabetes may be slowed if a number of risk factors are controlled especially in patients aged > 45 years, or those from a high-risk ethnic group (native American, Afro-American, Hispanic, Asian). Other risk factors include:

• Obesity (BMI > 27 kg/m²)
• Past history of gestational DM
• Existing impaired glucose tolerance test
• Accompanying hypertension
• Low high density lipids or increased triglycerides

Type 1 diabetes: Type 1 diabetes only accounts for between 5–10% of all cases, and has an incidence of about 0.4% in the European and American populations. Most patients present as children, although about 35% are identified as adults. There are two different aetiologies – autoimmune and immune-mediated (type 1A), or idiopathic (type 1B), with some patients showing various genetic markers and autoimmune antibodies against pancreatic cell islets, indicating an immunological basis to the disease. Diabetic ketoacidosis (DKA) is more common in type 1 than type 2 diabetic patients. The type 1 diabetic has an obligate need for insulin as there is usually an absolute insulin deficiency, although, in general, type 1 diabetics normally have a lower insulin requirement than the type 2 patients where there may be insulin resistance.

Type 2 diabetes: Type 2 diabetes usually presents in older patients, but is being seen increasingly in certain younger patient groups (especially native Americans, Afro-Americans and Hispanics). Type 2 DM accounts for about 90% of all diabetes (with a prevalence of about 6.0% in the USA, so equating to about 15–20 million of the USA population). The incidence has increased two-fold over the last decade! Type 2 DM occurs because of a relative deficiency of insulin or peripheral resistance to insulin or excess hepatic glucose release. It is associated with a significant risk of accompanying cardiovascular disease, and hence the need for attention to blood pressure and lipid control in these patients (see later). Most type 2 diabetics produce adequate amounts of insulin to prevent ketosis occurring, but they are at risk of hyperosmolar coma (see later).

Co-morbidities in the surgical diabetic patient

a. Cardiovascular disease: There is an increased incidence of a number of cardiovascular co-morbidities associated with diabetes including arterial hypertension, coronary artery disease, peripheral vascular disease, systolic and diastolic left ventricular dysfunction, and/or leading to congestive cardiac failure. Cardiac pathologies are the main cause of death in about 80% of diabetic patients.

Many diabetic patients are found to have co-existing hypertension at the time of diagnosis; in these patients, it seems that modest blood pressure control is more important than chronic tight glycaemia control. For example, the UK Prospective Diabetes Study (UKPDS) found that reduction of blood pressure in diabetic patients resulted in a decrease in cardiovascular and cerebrovascular events, while the Hypertension Optimal Treatment (HOT) study demonstrated that aggressive diastolic pressure reduction causes reduced cardiovascular mortality.12

The current aim of management in the UK and USA of blood pressure in diabetics is a pressure < 130/80; often multiple drugs will be needed to achieve this. In type 2 diabetic patients, hypertension may also be associated with the development of a progressive nephropathy, hyperinsulinaemia and insulin resistance, arterial vascular non-compliance, and chronic extracellular hypervolaemia (leading to the so-called Syndrome X or Insulin Resistance Syndrome).6

Between 8–31% of type 2 diabetic patients have asymptomatic coronary artery disease, and there is a greater incidence of cardiac death after myocardial infarction than in the non-diabetic subject. In the surgical patient, we should suspect the presence of myocardial ischaemia or infarction if there occurs unexplained
confusion, hypotension, dysrhythmias, hypoxaemia, or non-specific electrocardiograph (ECG) changes. Myocardial ischaemia or infarction may be clinically silent in the patient with DM if there is an associated autonomic neuropathy.

Diabetic autonomic neuropathy will present in its earliest stages as a lack of variation of the cardiac rate, with a tendency to higher than average resting heart rates. Other features include postural hypotension, and intra-operative episodes of bradycardia and hypotension occurring unexpectedly without apparent precipitating causes. Cardiac neuropathy is present in between 20 and 40% of all diabetics and is associated with a poor prognosis.

Left ventricular dysfunction is found in diabetic patients at an incidence of about 4–5 times that in the general population, and is often associated with hypertension and left ventricular hypertrophy, endothelial dysfunction, obesity, autonomic neuropathy, and metabolic complications secondary to hyperglycaemia and hyperlipidaemia. (Because of these various associated risk factors, many diabetic patients will receive other drug therapies including ACE inhibitor, low-dose aspirin, and lipid regulating drugs – all are beneficial in patients with the combination of diabetes DM and high cardiovascular risk.)

The high incidence of associated cardiovascular disease suggests that stress testing in diabetic patients presenting for major surgery should be a routine where there are ANY TWO other risk factors (e.g. smoking, increased cholesterol or a dyslipidaemia, hypertension, a family history of coronary arterial disease, or males > 40 years of age). However, the role of perioperative beta-blockade in high-risk diabetic patients undergoing major non-cardiac surgery has recently been questioned by the negative results of the DIPOM study.5

b. Cerebrovascular disease: Diabetic patients have increased incidences of cerebrovascular disease and stroke as a result of the accompanying increased frequency of hypertension, dyslipidaemia, accelerated atherosclerosis and abnormal endothelial proliferation.

c. Renal disease: Diabetes mellitus is the leading cause of renal failure in the USA. Endstage renal disease occurs in about 30% of type 1 and up to 20% of type 2 diabetic patients. Prevention of further dysfunction is achieved by control of hyperglycaemia and hypertension; avoiding nephrotoxic drugs and contrast media, and maintaining adequate hydration especially in the perioperative period.

Drug treatments and the surgical diabetic patient

a. Diet: Most diabetic patients controlled by diet alone will require no special medication pre-surgery, however those undergoing major surgery may progress to need insulin therapy at least transiently in the postoperative period.

b. Oral drugs:

1. Sulphonylureas act to increase pancreatic ß-cell sensitivity and augment insulin secretion by binding to ATP-dependent K+ channels. They may also have some long-term effects by increasing the numbers of insulin receptors on cell membranes. Variable duration of action (usually less than 24 hours) but chlorpropamide has an effect up to 72 hours.

First generation – tolbutamide, chlorpropamide
Second generation – include glibenclamide, glyburide, glipizide, glimepiride

Both first and second generation drugs should be withheld on the day of surgery. These drugs can safely be combined with insulin therapy.

2. Biguanides (metformin) act on the liver to decrease glucose output and on extrahepatic sites to increase glucose utilisation by a shift from oxidative to anaerobic metabolism and decreasing gluconeogenesis. Metformin only acts in the presence of some residual functioning beta-pancreatic islet cells; it may also inhibit intestinal glucose absorption.

Metformin is associated with a lower risk of perioperative hypoglycaemia than is the case with the sulphonylureas, but it should still be stopped for 24 hours pre-surgery, and its use avoided postoperatively in patients with renal or hepatic insufficiency.

3. Alpha-glucosidase inhibitors (e.g. acarbose) decrease gastrointestinal digestion and absorption of saccharides and in turn glucose synthesis. It is useful in the reduction of postprandial hyperglycaemia in type 1 DM, and may be an adjunct to metformin and sulphonylureas. Present evidence indicates no need to stop α-glucosidase inhibitors pre-surgery.

4. Thiazolidinediones (e.g. pioglitazone, rosiglitazone) act on extrapancreatic sites to reduce peripheral insulin resistance and hence increase insulin sensitivity, and on the liver to inhibit gluconeogenesis. They act by activating specific nuclear receptors termed PPAR-gamma (peroxisome proliferator activated receptor gamma). The thiazolidinediones are given either alone, or in combination with metformin or a sulphonylurea. Inadequate drug response may indicate failure of intrinsic insulin release.

5. Meglitinides (e.g. repaglinide, nateglinide): These benzoic acid derivatives stimulate insulin secretion by binding to ATP-dependent K+ channels in pancreatic cells. Repaglinide has a rapid onset and short duration of effect, and is therefore given before meals.

Both thiazolidinediones and meglitinides should be stopped on the day of surgery.

c. Insulins

These may best be classified based on their onset and duration of action.

- Rapid – lispro, aspart
- Short acting: regular
- Intermediate acting: NPH and lente
- Long acting: ultralente and glargine

Mixtures of short and intermediate acting drugs: biphasic insulin aspart and lispro; biphasic isophane.

Although tds regimens may be used for the introduction of insulin therapy, long-term strategies include:

i. Intermediate-acting insulin plus a short-acting insulin given together in the morning and evening.

ii. Intermediate- or long-acting insulin at bedtime and injections of short-acting insulin before each meal.

iii. Long-acting insulin in the morning plus short-acting insulin in the morning and evening.

iv. Long-acting insulin in the morning with or without a short-acting insulin in the morning.
The most suitable insulin regimens for the perioperative period have not been clearly defined, and a number of different regimens have been described.

**Anaesthesia in the surgical diabetic patient**

In general, the strategy for glucose control among anaesthetists is far from consistent, with variability in the desired endpoint. Preoperative assessment should include a full electrolyte, urea and creatinine screen, blood count with white cell differential, chest radiograph and electrocardiogram. Patients receiving other coincidental therapy should have them optimised before surgery. In the presence of uncontrolled diabetes, the plasma and whole body potassium levels may be decreased; and therefore additional supplementation must be given pre-surgery.

**Strategies for control of blood glucose concentration**

**a. Elective surgery in non-insulin dependent diabetics:**

Most patients will have sufficient endogenous insulin secretion to carry them through minor surgery (i.e. surgery not involving penetration of a body cavity or transection of a major limb bone) and avoid the need for transient insulin therapy. For major surgery, exogenous insulin will usually be necessary to avoid the development of ketosis.

**b. Elective surgery in the insulin dependent diabetic:**

The ‘laissez-faire’ approach of Fletcher et al (1965) where there is no active management of the blood glucose concentration is no longer appropriate for the perioperative care of these patients. The various approaches adopted are based on either regular small dose administration of IV insulin or an infusion of insulin with the simultaneous infusion of 5% dextrose (with adjustment of rates of infusion of insulin and/or glucose based on frequent blood glucose estimations), or the glucose-insulin-potassium regimen of Alberti. Blood glucose estimations should be undertaken hourly until the blood glucose is either well-controlled or enteral feeding can be re-started.

If the patients are already on long-acting insulin preparations as part of their care, this can be safely given the evening before surgery to achieve basal normoglycaemia and then half-hourly intravenous boluses of a rapid acting insulin preparation (based on patient’s weight, height and existing blood glucose level) given to maintain the perioperative plasma glucose concentration between 4 and 8 mmol/l.

Other regimens include:

1. Administration of half or two-thirds of the patient’s usual intermediate acting insulin dose subcutaneously
2. Subcutaneous insulin pumps
3. Use of the artificial pancreas

**Outcome measures and complications of treatment**

Beyond the avoidance of hypoglycaemia, there is little reason to believe that any state other than euglycaemia (80–110 mg/dl or 4.5–6.0 mmol/l) is best for the perioperative patient. The benefits of glucose control and associated insulin therapy include decreased osmotic diuresis, enhance innate immunity, improved endothelial function, and less impact on ischaemic tissues. These benefits occur through decreased lipolysis and less generation of free fatty acids (these act to exacerbate myocardial ischaemia and arrhythmias), inhibition of deleterious growth factors (e.g. AP-1, EGR-1), enhanced production of nitric oxide synthase, inhibition of pro-inflammatory mediators including cytokines, chemokines, acute phase proteins and adhesion molecules. There is also some evidence linking chronic hyperglycaemia and the development of end-organ pathology in the long-term complications of diabetes.

There are several studies examining the effect of glycaemic control on patient outcome in the perioperative period. For example, in the study of patients randomised to intensive insulin (glucose 80–110 mg/dl) vs conventional therapy (glucose 180–200 mg/dl), Van den Berghe and colleagues found a significant reduction in mortality in critically ill ICU patients in the group where the glucose concentration was tightly controlled. Furnary and colleagues showed a similar benefit of improved glycaemic control in patients undergoing coronary artery bypass surgery. In two separate ICU studies (one retrospective, the other prospective), Krinsley et al showed an association between hyperglycaemia and mortality. Similar findings have been shown when examining the effect of intraoperative glycaemic control and severe morbidity in cardiac surgical patients.

Other studies in non-cardiac surgical patients also show an influence of diabetes mellitus on outcome. While Raby et al failed to show any association between diabetes and intra- and postoperative myocardial ischaemia, Hollenberg et al found postoperative myocardial ischaemia to occur more frequently in treated diabetic patients. Based on further data from the same VA study, Browner et al failed to find an association between diabetes and in-hospital and long-term mortality.

Although not the primary aim of our case-control studies using data from the Oxford Record Linkage Study, we found no association between diabetes and 30 day cardiac death following either elective and emergency/urgent non-cardiac surgeries. More recently, Jeger et al examined long-term mortality after major cardiovascular surgery in patients with diabetes and coronary artery disease. Mortality was only increased in patients treated with oral hypoglycaemics, suggesting a possible beneficial effect of insulin per se.

To date, there are no other prospective data to show that intraoperative glycaemic control is associated with improved outcome. Hence there are still five key questions to be answered in respect of the care of diabetic patients undergoing surgery:

1. Is good glycaemic control relevant to all types of surgical patient? If tight glycaemic control is needed, what level of blood glucose should we aim for?
2. In the emergency case, does the duration of the presenting illness correlate with the need for tighter diabetic control?
3. Is the benefit of better outcome in diabetic patients due to infusing glucose, infusing insulin or both?
4. Does early feeding help (as suggested by the work of Van der Berghe)
5. Does insulin resistance increase the morbidity rate?

Another key issue is how and by whom should the glucose be managed during the perioperative period?

**Potential metabolic complications associated with diabetes in the surgical patient**

1. **Ketoacidosis (DKA)**

DKA may present to the anaesthetist either in the intensive care unit or in the emergency room as an acute abdomen. Diagnosis is suggested clinically by drowsiness, dehydration, the smell of acetone on the breath, deep sighing respiration caused by the metabolic acidosis, gastric dilatation and hypotension.
There are two main defects in these patients – hyperglycaemia and ketonaemia. The former is due to a combination of increased hepatic glucose production and decreased peripheral glucose uptake. The ketonuria and acidosis are directly due to the build-up in the body of the ketocids: ß-hydroxybutyrate and acetooacetate. Together the two factors initiate an osmotic diuresis that causes intravascular dehydration and urinary electrolyte loss. The ensuing hyperosmolality further exaggerates the intracellular dehydration. Investigations often reveal a blood glucose in excess of 20 mmol/l (due to reduced renal glucose clearance), elevated plasma ketone levels, elevated white cell counts, and electrolyte and urea abnormalities (increased potassium, creatinine and urea, normal or low sodium). Management includes rehydration with volume expanders (both colloid and crystalloid), and additional potassium supplementation as needed. Surgery should not be undertaken until the blood glucose level is less than 15 mmol/l. The severe acid-base disturbances must also be corrected pre-surgery, as acidosis depresses respiration, and adversely affects cardiovascular function causing reduced myocardial contractility, peripheral vasodilatation and ventricular arrhythmias.

2. Hyperosmolar non-ketotic coma (HONKC)

This is increasingly recognised as a complication in the post-surgical diabetic patient. There are various aetologies of HONKC:

i. In susceptible patient populations i.e. in patients with previously undiagnosed diabetes, patients with pancreatitis and post-pancreatectomy patients, in uremic patients and patients on dialysis, patients undergoing cardiopulmonary bypass.

ii. Following administration of excessive exogenous glucose loads due to parenteral or enteral feeding, or to infusion of 50% glucose solutions.

iii. As a result of concurrent therapies taken by the patient including steroids, adrenaline and other sympathomimetics, diuretics (especially thiazides and diazoxide).

The commonest cause of HONKC is secondary to the development of intraoperative hyperglycaemia. In addition to the hyperglycaemia, the patients show signs of hypovolaemia and confusion. Because of the confusion, there is an inability to cope with the hypovolaemia by increased fluid intake, and hence severe dehydration occurs. Plasma urea is significantly elevated (due to the combination of a decreased blood volume and reduced cardiac output), and the serum osmolality > 320 mosm/kg. This may lead to other important complications including vascular thromboses. Overall mortality is about 50%.

3. Lactic acidosis

This may occur in diabetic patients due either to surgical or anaesthetic related hypotension and poor tissue perfusion, or may be drug induced due to medicants such as metformin, parenteral feeding with fructose or sorbitol, or acute ingestion of ethanol or salicylates. Excessive levels may exceed 2 mmol/l. Again, mortality is high (50-80%).

4. Hypoglycaemia

This may develop intraoperatively or in the postoperative period as a result of insulin overdose, or the residual effects of long-acting orally administered hypoglycaemic drugs. The incidence of perioperative hypoglycaemia is greater in patients suffering from malnutrition or malabsorption syndromes, severe liver disease, reduced glucoseogenesis secondary to alcoholism, or increased tissue glucose uptake secondary to failure of catecholamine secretion or ß-adrenoreceptor blockade.

In the conscious patient, hypoglycaemia presents as anxiety, hyperactivity and coma with cardiovascular signs of sympathetic overactivity. The diagnosis in the anaesthetised patient is more difficult and depends on regular blood glucose determinations.

5. Delayed wound healing, and wound infection

High postoperative blood glucose levels are associated with impaired white cell function. Some studies have suggested increased incidences of wound infection in the diabetic patient, but this has not been substantiated in controlled trials.

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