# Diabetes care after pancreatic surgery

*Laura Woodcock*

**In the absence of specific guidelines for patients who develop diabetes as a result of pancreatic surgery, this article discusses the most appropriate therapeutic options for this group. Pancreatogenic diabetes, including that related to total pancreatectomy and distal pancreatectomy, is defined, outlining incidence rates and explaining the need for current evidence-based guidelines on its management. Three key components – insulin, glucagon and education – are prioritised. Potential improvements and alternative approaches to managing this cohort, and the impact they may have on care in the future, are also discussed.**

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### Article points

1. Diabetes resulting from complete or partial resection of the pancreas is characterised by absence of insulin, glucagon and other pancreatic hormones.
2. Exogenous insulin therapy is required; however, insulin dose requirements are typically lower than in people with type 1 diabetes.
3. People undergoing pancreatic surgery should be evaluated by the diabetes team before surgery and receive education into the management of their potential new diabetes postoperatively, and should have long-term follow-up with the diabetes team.

### Key words

- Comorbidities
- Distal pancreatectomy
- Pancreatogenic diabetes
- Total pancreatectomy
- Type 3c diabetes

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First performed in 1942 for a patient with a symptomatic insulinoma (Priestley et al, 1944), total pancreatectomy (TP) is now used for a number of indications, including hereditary pancreatitis, end-stage chronic pancreatitis, pancreatic adenocarcinoma, neuroendocrine tumours and neoplasia with malignant potential, such as intraductal papillary mucinous neoplasm (Parsaik et al, 2010). Diabetes induced by TP is characterised by complete insulin deficiency, similar to typical cases of type 1 diabetes (Jamil et al, 2012). Insulin deficiency secondary to TP is inevitable, and it can result in wide, fast, unpredictable and inexplicable swings in blood glucose concentration, often resulting in ketoacidosis or hypoglycaemic coma (Maker et al, 2017).

The management of endocrine insufficiency post-TP has improved over time; however, many aspects of TP-induced diabetes are still not well defined. The treatment of diabetes in these individuals usually involves the therapies used to treat type 1 diabetes; however, no specific guidelines have been developed for its management, either immediately after pancreatic surgery or over the long term (Scavini et al, 2015). With added endocrine and exocrine abnormalities accompanying TP, including an absence of functional glucagon and pancreatic exocrine deficiency resulting in malabsorption, these patients can be difficult to manage. A prompt diagnosis of this type of diabetes is necessary for the immediate implementation of appropriate therapeutic options, in order to prevent unnecessary complications (Ewald and Bretzel, 2013).

## Pancreatogenic diabetes

As defined by the American Diabetes Association (ADA, 2014), people who have undergone TP suffer from type 3c diabetes, also called pancreatogenic diabetes. This type of diabetes is unique in that the individual is completely deprived of both the exocrine and the endocrine functions of the pancreas. Insulin and glucagon, as well as other pancreatic hormones, are completely lacking (Niwano et al, 2018). Pancreatogenic diabetes exposes people who have undergone TP to life-threatening complications over the short and long term, making its medical treatment quite challenging. Pancreatogenic diabetes is caused by destruction of the pancreas and can also develop

**Page points**

1. Proposed criteria for the diagnosis of pancreatogenic diabetes are the presence of pancreatic exocrine insufficiency, evidence of pancreatic pathology on imaging and absence of type 1 diabetes autoantibodies.
2. People who undergo total pancreatectomy appear certain to develop pancreatogenic diabetes unless they undergo simultaneous islet cell transplantation.
3. People who undergo distal pancreatectomy are less certain to develop diabetes, with risk factors including the underlying pancreatic disease, the amount of pancreas resected and the length of time postoperatively.

after pancreatic resection or chronic pancreatitis, leading to deficiency in pancreatic hormones (Maeda and Hanazaki, 2011).

In order to improve its recognition, Ewald and Bretzel (2013) have proposed diagnostic criteria for type 3c diabetes. According to their criteria, the diagnosis requires the following:

1. Presence of pancreatic exocrine insufficiency.
2. Evidence of pathological pancreatic imaging (by endoscopic ultrasound, MRI or CT).
3. Absence of autoantibodies associated with type 1 diabetes.

The diagnosis may be further supported by evidence of deficiencies in pancreatic polypeptide, incretin or insulin.

## Pancreatogenic diabetes incidence rates

### Total pancreatectomy

In recent years, the frequency of and indications for TP in the treatment of pancreatic diseases has increased. This could be due to early diagnosis of premalignant lesions and the increased safety of pancreatic surgery which, combined with advances in insulin formulations, has reduced the morbidity and mortality risk of the procedure (Murphy et al, 2009). Five studies have reported on people who underwent TP, with cohort sizes ranging from 14 to 141 people and follow-up ranging from 18 months to 24 years (Stauffer et al, 2009; Parsaik et al, 2010; Jamil et al, 2012; Barbier et al, 2013; Roberts et al, 2013). Of the respondents who survived the follow-up period, all developed postoperative diabetes.

The incidence of diabetes post-TP appears certain unless the patient receives a concomitant islet transplant. Islet cell transplantation (ICT) is a procedure which can be performed following TP, in which the surgeon then extracts and purifies islets from the pancreas. Within hours, the islets are infused through a catheter into the patient's liver. The goal is to give the body enough healthy islets to make insulin. Unfortunately, there is limited access to islet-processing facilities and expertise to carry out this procedure in Ireland. In addition to lack of resources, there are several other limitations to ICT, including the risk of non-functioning islets and progressive loss of islet function over time (Maker et al, 2017).

### Distal pancreatectomy

Distal pancreatectomy (DP) is a surgical operation for resection of both neoplastic and non-neoplastic lesions of the body and tail of the pancreas (King et al, 2008; Liu et al, 2017). The resection may include splenectomy or liver resection, depending on the nature and anatomical position of the lesion.

The minimal amount of residual pancreas necessary to preserve normal glucose homeostasis is unknown (De Bruijn and van Eijck, 2015). According to the literature, the incidence of new-onset diabetes after DP varies from 4% to 51% (Maeda and Hanazaki, 2011; Kwon et al, 2015; Hwang et al, 2017), depending on the underlying disease and the amount of pancreas being removed, factors that are associated with the endocrine function of the residual pancreas (Scavini et al, 2015). Sakata et al (2011) suggest that the surgeon should preserve pancreatic parenchyma as much as possible to maintain a good endocrine and exocrine pancreas if sufficient tumour eradication is achieved.

In addition, the length of time postoperatively has an impact on the incidence of pancreatogenic diabetes. De Bruijn and van Eijck (2015) reported that the incidence of new-onset diabetes was 17% within 6 months of DP; however, this increased to 36% after longer follow-up periods. Similarly, King et al (2008) found that the risk of diabetes after DP was relatively low immediately postoperatively, with 5–20% of patients developing new-onset diabetes in the short term and 40–50% developing it up to 7 years after the surgery. Furthermore, the single biggest risk factor for type 2 diabetes is ageing, so with increased age post-pancreatectomy, rates of diabetes would be expected to rise. Thus, the development of pancreatogenic diabetes should be checked periodically during the follow-up period.

## Insulin

As previously mentioned, the diabetic state induced by TP is characterised by complete insulin deficiency, confirmed by the absence of C-peptide in the serum, which puts the patient in immediate risk of hyperglycaemia unless exogenous insulin is supplied (Maker et al, 2017). Unfortunately, all large diabetes clinical trials studying glycaemic control have excluded participants with pancreatogenic diabetes. Without an evidence-

based algorithm to aid in the management of these patients, it is consistently recommended that insulin dosing guidelines for type 1 diabetes be followed (Rickles et al, 2013).

However, Niwano et al (2017) compared the total daily insulin requirements of people post-TP and those with type 1 diabetes, observing a marked difference between the two groups. The total daily insulin requirement and basal insulin dose, but not the prandial insulin dose, were significantly smaller in post-TP patients than in people with type 1 diabetes. In particular, the basal insulin dose in the TP group was as low as 3.7 units/day, less than a third of the dose required in the type 1 diabetes group (11.4 units/day). The basal insulin as a percentage of total daily dose was also significantly smaller in the TP group than the type 1 diabetes group (15.8% vs 32.9%).

Parsaik et al (2010) completed a meta-analysis of the literature and concluded that patients post-TP need less insulin per day compared to people with type 1 diabetes. They found severe hypoglycaemia to be a significant problem, occurring in 79% (*n*=37) of individuals on simple insulin therapy (one to two injections daily) and in 26% of those on complex insulin therapy (either an insulin pump or three to four injections daily). Of 37 patients with reported hypoglycaemia, 41% (*n*=15) developed severe, potentially life-threatening hypoglycaemia requiring third-party assistance.

### Towards a treatment algorithm

These findings demonstrate that people with pancreatogenic diabetes need much lower doses of insulin than those with type 1 diabetes and, consequently, that specific dosing guidelines are needed for this cohort. In the absence of generally accepted guidelines, Maker et al (2017) suggest a postoperative treatment algorithm for patients following TP, based on the ADA (2017) guidelines for diabetes care in the hospital. They suggest commencing intravenous insulin immediately postoperatively at a rate of 0.1 units/kg/hour, together with intravenous dextrose fluids. Requirements can thereafter be calculated and then be 60–80% replaced in the subsequent days by one half basal and the other half rapid-acting insulin. The authors also stress the importance of administering the basal insulin dose 1–2 hours before discontinuation of the insulin infusion.

Reviewing patients who underwent DP, Liu et al (2017) found that the majority initially used low-dose variable subcutaneous insulin injections, which seemed to be safe and effective for immediate postoperative glycaemic control. Most patients received a total daily dose of <0.1 units/kg after DP. Patients post-DP need to be treated with much lower doses of insulin than are recommended for other inpatient populations (Rubin et al, 2011; Umpierrez et al, 2011). These findings suggest that 0.05–0.20 units/kg is an appropriate dose range for this cohort. This recommended dose range would help lower the risk of hypoglycaemia among this vulnerable population (Liu et al, 2017).

## Glucagon

Glucagon is a well-known counter-regulatory hormone of insulin, and is completely lacking in post-TP patients (Niwano et al, 2017). The function of glucagon is to increase blood glucose concentration via stimulation of hepatic gluconeogenesis and glycogenolysis, in addition to stimulation of insulin secretion (Klover and Mooney, 2004). Due to the reduction or absence of the glucagon-producing alpha-cells that are mainly located in the body and tail of the pancreas, patients undergoing pancreatic surgery may be more vulnerable to severe hypoglycaemia (De Bruijn and van Eijck, 2015). According to a few studies, insulin requirements are usually lower than expected after TP because of an increase in expression of peripheral insulin receptors and a lack of glucagon response (Scavini et al, 2014; Maker et al, 2017; Niwano et al, 2017).

Furthermore, patients undergoing major pancreatic resection are more sensitive to exogenous insulin than people with type 1 and type 2 diabetes (Scavini et al, 2014). They experience rapid swings of glucose levels, varying from hyperglycaemia because of unsuppressed hepatic glucose production, to severe hypoglycaemia after administration of exogenous insulin because of the lack of glucagon response (Scavini et al, 2014). Hence, the therapeutic window in maintaining euglycemia is narrowed, resulting in problematic glycaemic control and increased susceptibility to hypoglycaemia (Maker et al, 2017).

**Page points**

1. While people with pancreatogenic diabetes require exogenous insulin, their dose requirements are significantly lower than in people with type 1 or type 2 diabetes.
2. Because they are unable to produce glucagon as well as insulin, they are more sensitive to insulin therapy and are at increased risk of hypoglycaemia.

**Page points**

1. People undergoing pancreatic surgery should be evaluated by the diabetes team before surgery and receive education on the management of their potential new diabetes postoperatively.
2. Referral for diabetes education before surgery, followed by surgical re-evaluation to determine whether the patient has appropriate understanding, support and resources, is recommended.
3. The importance of nutrition, appropriate caloric intake, and enzyme and vitamin replacement is also important to review with the patient pre- and postoperatively.

## Education

A patient undergoing TP requires intensive diabetes education, including dietary advice, and follow-up at a specialist diabetes centre. Among the studies reviewed in this article, there was considerable disparity in the education patients received both pre- and postoperatively. Most studies recognised the importance of long-term follow-up by a diabetes specialist team; however, they did not mention any preoperative assessment (Kim et al, 2011; Barbier et al, 2013; De Bruijn and van Eijck, 2015; Hwang et al, 2017). Liu et al (2017) found that only a small proportion of patients received consulting services from the diabetes team (4.9%) and dietitian (28%) during hospitalisation. In contrast, Stauffer et al (2009) and Jamil et al (2012) found that all patients were assessed by the inpatient diabetes education and nutritional management team, both preoperatively and immediately postoperatively.

The author feels it is critical to preoperatively identify patients who are incapable or unwilling, for any reason, to monitor and maintain glycaemic control. Maker et al (2017) feel that inability to perform these tasks and lack of understanding on the part of the patient and/or family are contraindications for recommending or performing TP. In their experience, a referral for patient education before surgery, followed by surgical re-evaluation to determine whether the patient has appropriate understanding, support and resources preoperatively, has significantly reduced mortality and morbidity.

The evidence also shows improved outcomes with follow-up diabetes education with the diabetes nurse specialist, dietitian and endocrinologist (Haas et al, 2012). With the increased risk of hypoglycaemia, combined with so many other aspects to consider, such as injection technique, self-monitoring of blood glucose, exercise, travel, ketones, driving guidelines and alcohol, close collaboration with a diabetes specialist is essential to provide the best care to patients after pancreatic surgery. Scavini et al (2015) argue that improving patients' awareness and concordance, combined with advanced insulin formulations and delivery systems, will contribute to the improvement of glycaemic control and stability over time. Additionally, they suggest that readmission rates are significant and indicative that these individuals require additional input from outpatient endocrine teams.

### Dietitian input

In addition to education on general diabetes management and glycaemic control, the importance of nutrition, appropriate caloric intake, and enzyme and vitamin replacement is important to review with the patient pre- and postoperatively. This includes recommendations on types of carbohydrate, adequate protein intake and appropriate exocrine enzyme replacement. A recent review by Duggan et al (2017) provides detailed dietary advice for these patients (available here). The authors prioritise prevention of hypoglycaemic events and the provision of education regarding hypoglycaemia symptoms and treatment. Furthermore, they express the importance of loss of exocrine function and the need for pancreatic enzyme replacement.

## Limitations of the evidence

Unfortunately, major landmark studies such as the UK Prospective Diabetes Study and the Diabetes Control and Complications Trial excluded people with pancreatic disease, so there is very little evidence regarding incidence rates or best clinical practice in this group. Most of the data on clinical outcomes in people who underwent TP for various reasons are based either on a large number of patients enrolled over a long period or on a small number of cases enrolled over a short period (Pezzilli, 2012). With cohorts limited in number and size, many of the studies were retrospective, with a result that patients were excluded from studies due to insufficient data.

Pancreatogenic diabetes is a potential cause of microvascular complications, including retinopathy, neuropathy, nephropathy, and macrovascular complications, but there are limited long-term data on glycaemic control and end-organ complications in such patients. Parsaik et al (2010) performed a meta-analysis to address these shortcomings; however, they found no published studies addressing microvascular or macrovascular complications. Longitudinal follow-up would be required to confidently compare organ-specific diabetes-related complications.

## Conclusion

The need persists for the development of appropriate endocrine postoperative strategies. Research suggests that daily insulin requirements are usually less in pancreatogenic diabetes than in type 1 diabetes, and that these patients may be more vulnerable to severe hypoglycaemia; however, there is no consensus regarding treatment pathways specifically for this type of diabetes. It is clear that a simple, evidence-based guideline for immediate post-surgery glycaemic management is needed. However, this requires further research specifically aimed at these patients.

The healthcare professional should have detailed knowledge of the surgical procedure and its potential for diabetes complications postoperatively. A prompt diagnosis of pancreatogenic diabetes is necessary for the immediate implementation of appropriate therapeutic options. To prevent unnecessary complications, the healthcare professional should be familiar with the recognition and treatment of hypoglycaemia and hyperglycaemia. Given the risk of severe hypoglycaemia and, conversely, diabetic ketoacidosis, the healthcare professional should be very cautious and review the dose of insulin frequently to minimise patient risk.

People undergoing pancreatic surgery should be evaluated by the diabetes team before surgery and have sufficient insight into the management of their potential new diabetes postoperatively. Close collaboration with the diabetes outpatient service should be considered, for follow-up with an endocrinologist, a diabetes nurse specialist and a dietitian, for education, to optimise glycaemic control and further personalise insulin therapy. In people undergoing DP, the risk of endocrine insufficiency is not always certain, so it should be evaluated preoperatively, immediately after surgery, at discharge and then periodically during follow-up visits, since it may improve or worsen following surgery. ■


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