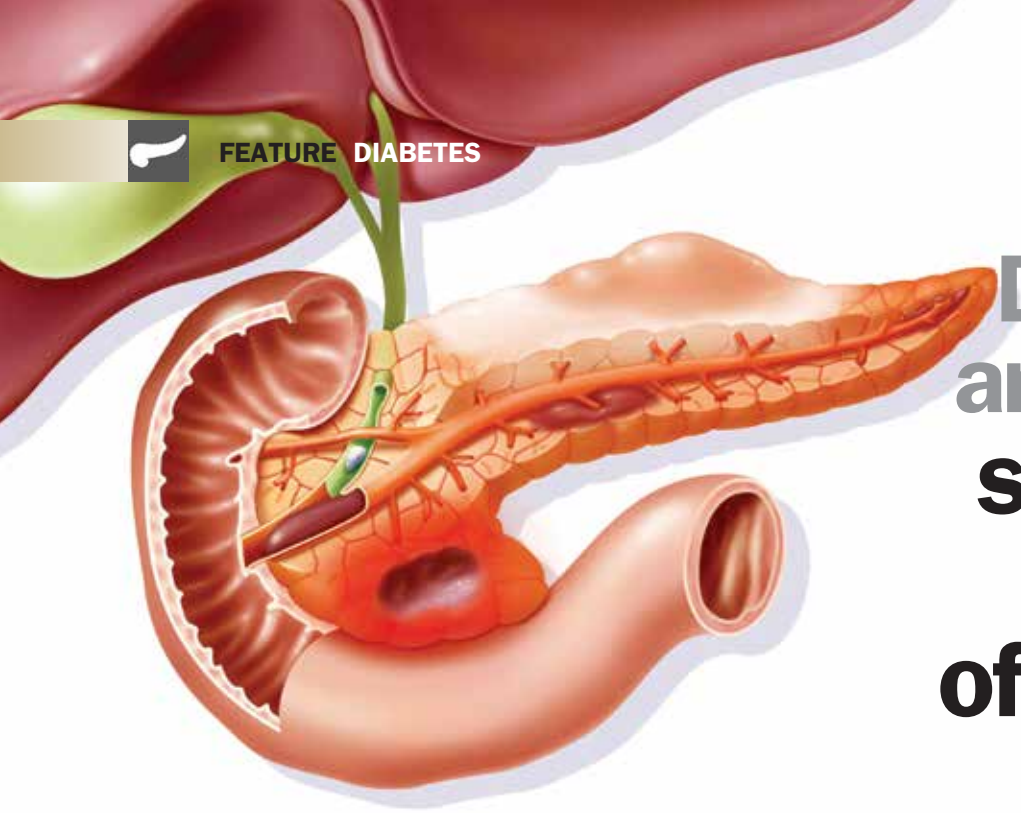

Diagnosing and treating secondary causes of diabetes

MIN LING MB BS
JEFF FLACK MB BS, FRACP, MM

Identifying and treating the underlying condition in secondary diabetes often improves the diabetes and may in some cases reverse it.

Key points

- **The main secondary causes of diabetes are genetic defects of beta cell function and insulin action, disease of the exocrine pancreas, endocrinopathies, drugs or other chemicals and infections.**
- **The mechanisms that cause secondary diabetes relate to the physiology and pathophysiology of the secretion of insulin and its action on target tissues.**
- **The goal and modalities of treatment for secondary diabetes are similar to those for the type 1 and type 2 forms of diabetes.**
- **Most cases of secondary diabetes require specialist management, often supported by a multidisciplinary diabetes care team, because of their uncommon and particular nature.**
- **The key to managing people with secondary diabetes is considering that the condition may be present, as new diagnoses may then occur associated with the cause and further options in therapy, including treating the primary cause, may become possible.**

ENDOCRINOLOGY TODAY 2014; 3(4): 18-23

Dr Ling is Endocrinology Advanced Trainee, and Associate Professor Flack is Director of the Diabetes Centre at Bankstown–Lidcombe Hospital, Sydney, NSW.

Diabetes mellitus (or diabetes) is a clinical syndrome of symptoms and signs with a biochemical definition, and has various underlying causes. Secondary diabetes is a broad category that covers diabetes associated with a wide range of diseases or conditions other than those associated with the three main types of diabetes (i.e. beta cell destruction, usually with absolute insulin deficiency, as in type 1 diabetes; progressive insulin secretory defect on a background of insulin resistance, as in type 2 diabetes; and diabetes diagnosed in pregnancy [gestational diabetes]). Secondary diabetes constitutes less than 2% of all cases of diabetes.

Generally speaking, in addition to various diseases that cause damage to the exocrine pancreas itself and result in reduced insulin secretion, the subcategories of secondary diabetes are:

- genetic, resulting in decreased insulin secretion or action
- hormonal, causing increased counter-regulation resulting in imbalanced glucose-lowering action of insulin, as seen in conditions with excessive levels of glucagon, catecholamines, cortisol and growth hormone
- chemical- or drug-induced, mainly causing impaired glucose tolerance through increased insulin resistance.

Due to their uncommon and particular nature, most cases of secondary diabetes require specialist management, often supported by a multidisciplinary diabetes care team. The key to managing people with secondary diabetes is often considering that the condition may be present, as new diagnoses may then occur associated with the cause and further options in therapy, including treating the primary cause, may become possible.

Classification of secondary diabetes

The American Diabetes Association (ADA) classification of secondary diabetes is shown in Box 1.[1] Several of the relatively common

causes of secondary diabetes are addressed in this article, namely genetic defects, pancreatic diseases, endocrinopathies and medications.

Causes of secondary diabetes

Genetic defects of beta cell function and insulin action: monogenic diabetes

In recent decades, several monogenic (single gene) disorders that are predominantly autosomal and dominantly inherited have been identified in people with diabetes. The first identified was a syndrome of early onset, dominantly inherited diabetes originally titled MODY (maturity onset diabetes of the young).[2] Eight types of MODY (MODY 1 to MODY 8) have been identified, of which MODY 2 and MODY 3 are the most common. MODY 2, or GCK-MODY, is caused by a defect in the glucokinase gene (*GCK*) whereas MODY 3 is caused by a defect in the hepatocyte nuclear factor-1α gene (*HNF1α).*

Other single gene disorders, of which approximately a dozen have been identified, are reported in neonatal-onset diabetes.[2] These may cause permanent or transient diabetes, with the latter occasionally recurring later in life.

A further rare group arises from genetic defects of insulin action. These include type A insulin resistance syndrome, lipoatrophic diabetes, leprechaunism and Rabson–Mendenhall syndrome.

Overall, patients with monogenic diabetes are quite heterogeneous and clinical characteristics are not reliable in predicting the underlying pathogenesis. Several members of the same family may have the same genetic defect but do not all develop diabetes; the reason for this is unclear.

Diagnosis of this group of patients remains important, as there is the potential to alter management and prognosis and to screen at-risk family members. In particular, patients with *HNF1α* mutations exhibit exquisite sensitivity to sulfonylureas and can be successfully treated with oral hypoglycaemic agents. However, profound hypoglycaemia can occur on exposure to even small doses of sulfonylurea and dose titration must be done carefully. Patients with *GCK* mutations are much less likely to develop complications of diabetes because they mainly have mild fasting hyperglycaemia without significant postprandial hyperglycaemia. Mutations of *GCK* are not associated with complications as the hyperglycaemia is very mild; thus if verified genetically, there is no need for treatment.

Clinical clues to the diagnosis include the features described above and the autosomal dominant nature of the disease. Genetic testing for MODY is not routinely accessible in Australia at the current time.

Diseases of the exocrine pancreas

The frequency of diabetes in various pancreatic conditions is summarised in Table 1.[3]

Acute pancreatitis

Acute inflammation of the pancreas can cause transient glucose level elevation, and a wide range of incidence (8 to 83%) of abnormal carbohydrate metabolism has been reported in acute pancreatitis.[4] Alcohol has a particularly damaging effect on pancreatic tissue, causing a high incidence of glucose intolerance. Hyperglycaemia has also been correlated with tissue necrosis in acute pancreatitis, and a higher mortality. Some 24 to 35% of patients have glucose intolerance and 12% have diabetes mellitus following a single bout of acute pancreatitis.[5]

Chronic pancreatitis

Chronic pancreatitis is an inflammatory condition affecting both digestive and endocrine pancreatic functions. Although glucose intolerance is frequent in patients with chronic pancreatitis, overt diabetes mellitus does not usually manifest until late in the course of the pancreatic disease: patients with chronic calcifying pancreatitis are at higher risk (60 to 70%) of developing diabetes and glucose intolerance than are patients with noncalcifying disease (15 to 30%).[6] Insulin therapy is required for diabetes caused by chronic pancreatitis because of the beta cell destruction. The concomitant damage to the

1. Aetiological classification of secondary diabetes (American Diabetes Association)*

A. Genetic defects of β-cell function
MODY 1, 2, 3, 4 etc, mitochondrial DNA, transient or permanent neonatal diabetes, others

B. Genetic defects in insulin action
Type A insulin resistance, leprechaunism, lipoatrophic diabetes, others

C. Disease of the exocrine pancreas
Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy, others

D. Endocrinopathies
Acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, others

E. Drug or chemical induced
Pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, dilantin, gamma interferon, others

F. Infections
Congenital rubella, cytomegalovirus, others

G. Uncommon forms of immune-mediated diabetes
Stiff-person syndrome, anti-insulin receptor antibodies, others

H. Other genetic syndromes sometimes associated with diabetes
Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence–Moon–Biedi syndrome, myotonic dystrophy, Prader–Willi syndrome, others

* Adapted from: American Diabetes Association. Diabetes Care 2014; 37(Suppl 1): 581-590.[1]

Table 1. Frequency of diabetes in pancreatic diseases*

Pancreatic disease	Frequency of diabetes (%)
Acute pancreatitis	8 to 83
Chronic pancreatitis	15
Chronic calcific pancreatitis	60 to 70
Pancreatic cancer	40
Partial pancreatectomy	20
Total pancreatectomy	100
Cystic fibrosis	13
Haemochromatosis	30 to 60

* Adapted from: Garger YB, et al. In: Poretsky L, ed. Principles of diabetes mellitus, 2nd ed; 2010.[3]

glucagon-secreting alpha cells also results in frequent hypoglycaemia, adding to management complexity.

Pancreatic cancer

In more than 40% of people with early stage pancreatic cancers, impaired glucose tolerance was reported before symptomatic detection of the tumour.[7] Important clues to the possibility of pancreatic cancer being present in people with diabetes include severe hyperglycaemia at diabetes diagnosis that is resistant to oral and insulin therapy, especially in people who are not overweight or obese and may have lost weight recently. A similar profile of deterioration can occur in some people with longstanding diabetes that was previously well controlled but has then markedly deteriorated. In such cases, pancreatic imaging can help make the diagnosis, although typically the cancer will have already become incurable at its diagnosis.

Pancreatectomy

Total pancreatectomy, primarily used for the treatment of pancreatic cancer with large lesions in the head of the pancreas, is associated with a high incidence of glucose intolerance. Compared with standard pancreaticoduodenectomy (Whipple procedure), the pylorus-preserving modification of the Whipple procedure and total pancreatectomy, pancreatic resections not involving the duodenum, such as distal pancreatectomy, are associated with a lower incidence of new or worsened diabetes.

In addition, pancreatic resection can cause endocrine abnormalities other than insulin deficiency. These include pancreatic polypeptide deficiency with preservation of glucagon production if the resection is proximal, and glucagon deficiency if the resection is distal. Defective production of glucagon increases susceptibility to hypoglycaemia through loss of counter-regulation, and pancreatic polypeptide deficiency can hinder hepatic insulin action, thereby contributing to hyperglycaemia. The results of hepatic insulin resistance with persistent endogenous glucose production plus enhanced peripheral insulin sensitivity often manifest in a brittle form of diabetes, which can be difficult to manage.[8]

Cystic fibrosis-related diabetes

Cystic fibrosis comprises a clinical triad of abnormalities involving the sweat glands, the exocrine pancreas and the respiratory epithelium. Cystic fibrosis-related diabetes, the principal extrapulmonary complication of cystic fibrosis, occurs in 15 to 30% of affected adults (mean age of onset, 18 to 21 years) and up to 1% of affected children.[9]

Cystic fibrosis-related diabetes is associated with decrease in pulmonary function, worsening nutritional status, increased morbidity and decreased survival. As it is primarily a condition of insulinopenia rather than insulin resistance, early treatment with insulin may decrease morbidity.

Pancreatic infiltrative diseases – haemochromatosis

Haemochromatosis (bronze diabetes) is a state of iron overload due to either hereditary or acquired causes. The acquired causes include transfusional iron overload anaemias (thalassemia major, sideroblastic anaemia and chronic haemolytic anaemia), chronic liver diseases (hepatitis C, alcoholic liver disease and nonalcoholic fatty liver disease [NAFLD]) and dietary or parenteral iron overload. Iron deposits in the pancreas result in fibrosis and secondary diabetes in 30 to 60% of patients with advanced disease. Iron excess seems to contribute initially to insulin resistance and subsequently to decreased insulin secretion as well as hepatic dysfunction.[10]

Hereditary haemochromatosis is a common gene defect disorder and affects about one in 200 Caucasians in the general community. Clinical clues to its presence in a person with diabetes include excessive lethargy even with relatively mild hyperglycaemia, with liver transaminase levels more than twice (and often four times) the upper limit of normal. In such cases, iron studies can be performed and elevated saturation or ferritin levels should lead promptly to haemochromatosis gene testing (available under the Medicare Benefits Schedule [MBS]).

Treatment for haemochromatosis-related diabetes is phlebotomy and, if necessary, oral antidiabetes drugs or insulin. If the haemachromatosis is diagnosed early and treated before organs are permanently damaged, diabetes can be prevented.

Other neoplasms

Endocrine tumours of pancreas non-beta cells and/or the gut that cause glucose intolerance include glucagonoma (hypersecretion of glucagon), somatostatinoma (hypersecretion of somatostatin), VIPoma (vasoactive intestinal peptide tumour), gastrinoma (hypersecretion of gastrin) and carcinoid syndrome.

Furthermore, liver diseases such as NAFLD, chronic hepatitis, and cirrhosis can also lead to diabetes via mechanisms of increased insulin resistance and inadequate insulin secretion.

2. Medications with the potential to cause glucose intolerance or diabetes*†

- Alcohol
- Atypical antipsychotics
- Beta blockers
- Beta interferon
- Calcium channel blockers
- Clonidine
- Cyclosporin
- Diazoxide
- Glucocorticoids
- HIV protease inhibitors
- Megesterol acetate
- Nicotinic acid
- Oral contraceptive pills
- Pentamidine
- Phenytoin
- Tacrolimus
- Thiazides
- Thyroid hormone

* Adapted from: Garger YB, et al. In: Poretsky L, ed. Principles of diabetes mellitus, 2nd ed; 2013.[3]

† Not a comprehensive list.

Endocrinopathies

The central role or action of insulin in metabolic regulation is modified or balanced by many other hormones, including glucagon, growth hormone, cortisol and adrenaline. Hence overproduction of these counter-regulatory hormones may induce hyperglycaemia, particularly where insulin secretion is already deficient; conversely, failure of secretion can predispose to hypoglycaemia, especially in people treated with insulin.

Coinciding endocrine dysfunction, although uncommon, should be considered in individuals with newly-diagnosed diabetes, and in those being treated for diabetes whose control becomes unstable for unknown reasons. Because the endogenous production of insulin continues, the metabolic disturbance is typically mild, and can often be reversed or ameliorated by treating the endocrine disorder.

Drugs

Many medications and chemicals are known to cause glucose intolerance or diabetes, by a wide range of mechanisms. Some of these are listed in Box 2.[3]

Administration of other hormones, particularly corticosteroids, may antagonise insulin action, whereas thiazides, notably diazoxide, may inhibit insulin secretion. In most cases, these medications serve more to unmask latent diabetes than to produce it, and their effects are relatively mild and reversible once the agent is withdrawn.

Other uncommon secondary causes

Other forms of diabetes due to secondary causes that are relatively less common than those described above are two rare immune-mediated manifestations and several genetic syndromes.

The two immune-mediated manifestations are insulin autoimmune syndrome, which is due to anti-insulin receptor antibodies, and the Stiff-Man or Stiff-Person syndrome, an autoimmune disorder of the CNS associated with autoreactivity to glutamic acid decarboxylase. The genetic syndromes include chromosomal disorders such as Down, Klinefelter and Turner syndromes, and the distinctive disorder Wolfram syndrome. Wolfram syndrome has several variants and, when fully expressed, is known as DIDMOAD (after its four common features of diabetes insipidus, diabetes mellitus, optic atrophy and deafness).

Diagnosis of secondary diabetes

The diagnosis of secondary diabetes is made in light of the typical clinical picture in each individual case, such as history of pancreatic disease, culprit medication usage or genetic test results, in addition to the meeting of the usual diagnostic criteria for diabetes mellitus (a fasting plasma glucose level of 7.0 mmol/L or above, or a random plasma glucose level or two-hour oral glucose tolerance test [OGTT] result of 11.1 mmol/L or above). A glycated haemoglobin (HbA_{1c}) level above 48 mmol/mol (6.5%) is now also acceptable for diagnosing diabetes (although not yet rebateable under the MBS), but caution is needed in interpreting HbA_{1c} test results in the presence of conditions affecting red blood cells or their survival time, such as haemoglobinopathies or anaemia.[11]

Practice points regarding secondary diabetes are listed in Box 3.

Screening for secondary causes of diabetes

Screening for secondary causes of diabetes should be considered in patients who:

- have features of typical endocrinopathy (Cushingoid, acromegalic or hyperthyroid), especially if the diabetes is newly-diagnosed (with or without high-insulin requirement)
- are being treated for diabetes but control becomes unstable for unknown reasons
- have a relevant pancreatic disease history
- have a relevant medication history, in particular use of glucocorticoids and antipsychotics
- have a strongly positive family history of diabetes, especially autosomal dominant pattern.

Management of secondary diabetes

The goals of diabetes control in patients with secondary diabetes are the same as those in patients with other types of diabetes (i.e. control of hyperglycaemia, management of risk factors and prevention and treatment of macrovascular and microvascular complications), but with the additional goal of identifying and then treating the underlying condition in the hope that this will largely improve or in some cases reverse diabetes.

3. Secondary diabetes: practice points

- Screen patients with diabetes for secondary causes if they have typical features of other endocrinopathies or their diabetes becomes uncontrolled without obvious cause.
- Pay attention to family history, pancreatic surgery/pathology and medication history.
- Correction of potentially reversible underlying conditions is always the first step, although only applicable to a relatively small percentage of patients.
- For most patients with diabetes from secondary causes, achieving good glycaemic control using individualised nonpharmacological plus pharmacological therapy with or without insulin is likely to be the mainstay of management.
  - Only low doses of sulfonylurea should be used in patients with type 3 maturity onset diabetes of the young (MODY 3) as severe hypoglycaemia may occur with 'normal' doses.
  - A single dose of isophane insulin (intermediate-acting) in conjunction with a morning dose of prednisolone can be initial therapy for typical afternoon hyperglycaemia in insulin-naive patients who are placed on corticosteroid therapy.
- Treatment targets and complication screening in patients with secondary diabetes are similar to those in people with type 1 or type 2 diabetes.

Treating reversible conditions

Treatment of an underlying condition may include surgery to remove responsible tumours, or withdrawal or dose reduction of offending medications.

Lifestyle modification

Similar to any case of type 2 diabetes, initial management for secondary diabetes should always consist of lifestyle modification (nutrition therapy, exercise, avoidance of smoking) and education about self-care, including self-monitoring of blood glucose levels.

Pharmacotherapy

For patients with diabetes in whom nonpharmacological therapy has failed, monotherapy with an oral antidiabetes drug may be initiated. Options include biguanides (metformin) as first-line therapy, and sulfonylureas as a second agent (except in cases of MODY 3, in whom only low doses of sulfonylureas are required). Sulfonylureas have no role in the situation where pancreatic tissue is damaged or removed, where insulin therapy will be required.

When oral agents fail to control diabetes, insulin therapy (with or without oral agents) is usually the next step. However, combination oral therapy with a dipeptidyl peptidase-4 (DPP-4) inhibitor or one of the newly approved sodium–glucose cotransporter-2 (SGLT-2) inhibitors could be considered provided adequate control of the plasma glucose level can be achieved.

Treatment targets

The targets of treatment in secondary diabetes are similar to those in other types of diabetes, that is:[12]

- HbA_{1c} – below or around 53 mmol/mol (7%), individualised to the patient
- blood pressure – below 140/80 mmHg
- lipid levels – LDL-cholesterol below 2.5 mmol/L, HDL-cholesterol above 1.3 mmol/L, triglycerides below 1.7 mmol/L.

All patients with secondary diabetes should be routinely monitored for complications, including retinopathy and neuropathy.

Conclusion

The common categories of secondary diabetes to consider in clinical practice are monogenic diabetes, exocrine pancreatic pathology, other endocrine disorders and the unwanted effects of medications. Ultimately, the explanation for the mechanisms that cause secondary diabetes lies in the basic physiology and pathophysiology of the secretion of insulin and its action on target tissues. Hence the goal and modalities of treatment for secondary diabetes are similar to those for the type 1 and type 2 forms of diabetes. **ET**

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37(Suppl 1); S81-S90.
2. Steck AK, Winter WE. Review on monogenic diabetes. Curr Opin Endocrinol Diabetes Obes 2011; 18: 252-258.
3. Garger YB, Joshi PM, Pareek AS, Romero CM, Seth AK, Fleckman AM. Secondary causes of diabetes mellitus. In: Porestsky L, ed. Principles of diabetes mellitus. 2nd ed. New York: Springer-Verlag US; 2010. p. 245-258.
4. Thow J, Semad A, Alberti KGMM. Epidemiology and general aspects of diabetes secondary to pancreatopathy. In: Tiengo A, Alberti KGMM, Del Prato S, Vranic M, eds. Diabetes secondary to pancreatopathy: International Symposium Proceedings (international congress series). Amsterdam: Elsevier Science; 1988. p. 7-20.
5. Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. World J Gastroenterol 2007; 13: 3090-3094.
6. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. Gastroenterology 2000; 119: 1324-1332.
7. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology 2008; 134: 95-101.
8. Slezak LA, Andersen DK. Pancreatic resection: effects on glucose metabolism. World J Surg 2001; 25: 452-460.
9. Brennan AL, Geddes DM, Gyi KM, Baker EH. Clinical importance of cystic fibrosis-related diabetes. J Cyst Fibros 2004; 3: 209-222.
10. Wilson J, Lindquist J, Grambow S, Crook ED, Maher F. Potential role of increased iron stores in diabetes. Am J Med Sci 2003; 325: 332-339.
11. D'Emden MC, Shaw JE, Colman PG, et al. The role of HbA1c in the diagnosis of diabetes mellitus in Australia. Med J Aust 2012; 197: 220-221.
12. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2014; 37(Suppl 1): S14-S80.

COMPETING INTERESTS: None.