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PEER REVIEWED FEATURE
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Autoimmune conditions associated with type 1 diabetes

Key points

- Autoimmune thyroid disease is the most common autoimmune endocrine disease in patients with type 1 diabetes.
- Coeliac disease affects about 5% of children with type 1 diabetes, and also occurs in adults.
- Hypoadrenalism is the main feature of the more common form of polyglandular autoimmune syndrome associated with type 1 diabetes.
- Unexpected hypoglycaemia in type 1 diabetes can be caused by undiagnosed hypothyroidism, coeliac disease, hypoadrenalism and, rarely, hypopituitarism.
- Features of pregnancy care in women with type 1 diabetes include tight glycaemic control preconceptionally and during pregnancy, and management of coeliac disease and pregnancy-related changes in associated hypothyroidism if present.
- Women with type 1 diabetes may develop more severe and/or additional autoimmune diseases after pregnancy.

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)
JESSICA PHILLIPS MB BS

People with type 1 diabetes are likely to have another autoimmune disease, and possibly more. The presence of these associated immune conditions should be sought, ideally at the time of diabetes diagnosis.

People with type 1 diabetes often also have one or more additional autoimmune diseases, most commonly autoimmune thyroiditis and coeliac disease. Using a case-based approach, this article reviews these associated autoimmune conditions and highlights the clinical situations that suggest they are present and the steps to diagnose and manage them.

The case

Amanda, 26 years old, has had type 1 diabetes since the age of 4 years and has just delivered her first child, a daughter, without problems. Amanda and her husband Steve are delighted and have decided to call their daughter Felicity. They are, however, concerned that she may have or get type 1 diabetes.

How likely is Felicity to develop type 1 diabetes?

Type 1 diabetes is caused by the autoimmune destruction of beta cells in the pancreas. The T-cell mediated destructive process is triggered by external stimuli in an individual with genetic susceptibility. The destructive process usually takes a considerable time (months to years) before enough beta cells are destroyed to lower maximal insulin secretion to a point where the blood glucose level rises and causes symptoms (Figure).

Although there is a genetic basis for type 1 diabetes, about 80% of incident cases have no family history. However, if there is a positive family history (as in Felicity's case), the lifetime risk of developing type 1 diabetes increases dramatically from the 0.4% (or one

Dr P. Phillips is a Consultant Endocrinologist at the QE Specialist Centre, Adelaide. Dr J. Phillips is a Senior Registrar at the Women's and Children's Hospital, Adelaide, SA.

in 250) risk in those with no family history to:[1]

- 6.0% in offspring of a parent with type 1 diabetes (as in Felicity's case)
- 5.0% in siblings (including dizygotic twins)
- 50% in the other monozygotic twin if one has type 1 diabetes.

Although Felicity's lifetime risk is increased 15-fold by her family history, her absolute risk is still not high (6%, or one in 17).

POSTPARTUM THYROIDITIS

The case continued

Amanda presents six weeks later because she is 'going to pieces'. She says she is anxious, irritable, restless and cannot sleep. She does look anxious to you. Her temperature is 37°C, blood pressure 115/70 mmHg and pulse rate 96 beats/min. On examination she has no sites of pain or tenderness but she is flushed and has a noticeable tremor.

What conditions associated with type 1 diabetes should you consider in Amanda, and what tests should you perform?

Amanda has one autoimmune condition and is likely to have others. Postpartum thyroiditis occurs in approximately 7% of women without type 1 diabetes, in up to 25% of those with type 1 diabetes and in over 40% of those with a history of previous postpartum thyroiditis or who are positive for thyroid peroxidase antibodies (anti-TPO).[2] This form of thyroiditis is similar to the more common subacute thyroiditis but is often painless (as opposed to being associated with pain radiating throughout the neck and to the jaw) and is more likely to result in permanent autoimmune hypothyroidism. There are three phases in the usual course of subacute thyroiditis:[3]

- a period of hyperthyroidism one to four months after delivery as the inflammatory process destroys the thyroid follicles, releasing stored triiodothyronine (T3) and thyroxine (T4) into the general circulation
- a period of transient hypothyroidism some two to eight weeks later, lasting two weeks to six months, when inflammation no longer releases stored thyroid hormone but the damaged thyroid gland cannot produce enough thyroid hormone
- a period of gradual recovery (weeks to months) during which the thyroid recovers normal function and levels of thyroid hormone become normal.

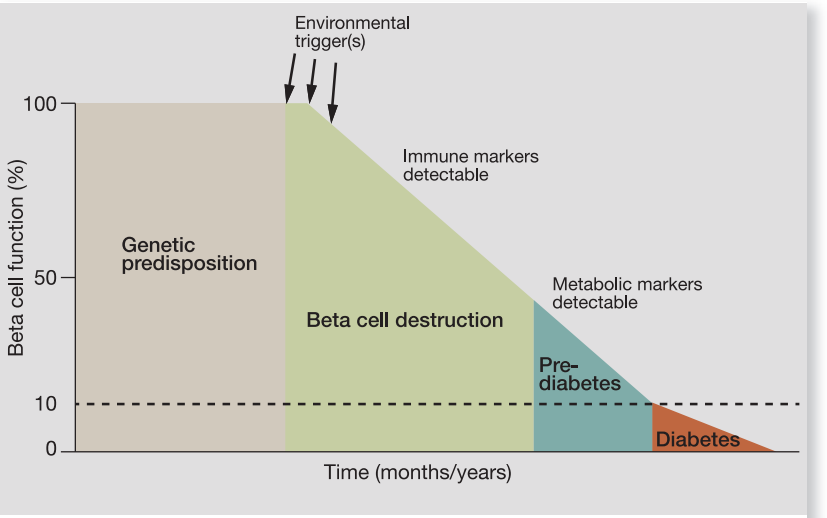

Figure. The natural history of type 1 diabetes. The genetic predisposition to type 1 diabetes is present at birth. In a minority of individuals with this increased genetic susceptibility, the environment and/or other external stimuli trigger autoimmune destruction of beta cells in the pancreas. Immune markers and then metabolic derangements become detectable long before clinical type 1 diabetes occurs, the signs and symptoms of this developing only when most of the beta cells have been destroyed.

About 25% of women with postpartum thyroiditis have the classical course of subacute thyroiditis, but 30% have only hyperthyroidism and 45% have only hypothyroidism (this then developing two to six months after delivery).[3] Women in whom permanent hypothyroidism can be expected usually have high titres of thyroid autoantibodies (anti-TPO, anti-thyroglobulin [anti-Tg]), are older and have had a female child.[4,5]

Tests for Amanda should include the following:

- tests for hyperthyroidism – thyroid function tests (levels of free T4, free T3 and thyroid stimulating hormone [TSH])
- tests for thyroid inflammation (measurement of erythrocyte sedimentation rate and C-reactive protein)

- tests to exclude other causes of hyperthyroidism (e.g. Graves' disease, toxic multinodular goitre) – thyroid ultrasound (to assess blood flow) and TSH receptor autoantibody levels. (A radionuclide scan with technetium would show no tracer uptake in the inflamed gland, as opposed to increased uptake in an overactive thyroid gland. However, this would not be suitable for Amanda as she would not be able to have close contact with or breastfeed Felicity for several weeks after the radionuclide exposure)
- tests for autoimmune thyroid disease – thyroid autoantibodies (anti-TPO and anti-TG).

The case continued

Amanda did have postpartum thyroiditis (her anti-TPO level was 365 IU/L; normal range, less than 50 IU/L), and she remained hypothyroid and required ongoing thyroid hormone replacement therapy.

DIAGNOSING TYPE 1 DIABETES

The case continued

Nine years later Amanda brings Felicity to the surgery because she thinks Felicity has diabetes. Felicity has been passing large amounts of urine and drinking lots of fluid day and night. When Amanda checked Felicity's fasting blood glucose level (BGL) before coming to the surgery it was 13.4 mmol/L. Laboratory determination of a random BGL gives a result of 15.2 mmol/L.

Is Amanda correct that Felicity has diabetes, and should you arrange for Felicity to have an oral glucose tolerance test?

Amanda is correct that Felicity does have diabetes but further tests are not needed to establish the diagnosis.

For a positive diagnosis of diabetes, two abnormalities are needed, either:

- one abnormal BGL value (fasting BGL, 7.8 mmol/L or higher; random or postprandial BGL, 11.1 mmol/L or higher) and symptoms suggestive of diabetes (e.g. the 'polys': poly-uria, -dipsia, -phagia), or
- two abnormal blood glucose values on two separate days.

In the USA, the glycosylated haemoglobin (HbA_{1c}) level is used for diabetes diagnosis, with the critical level being 6.5% or greater. This practice is likely to be accepted in Australia in the foreseeable future.

AUTOIMMUNE ENDOCRINE CONDITIONS

The case continued

Felicity adapted to her diabetes very well and has been managing her own blood glucose testing and basal bolus insulin schedule. Her glycaemic control has been reasonable (HbA_{1c} 6.8 to 8.1%) over the past three years. Recently, however, Felicity has been having many unexpected hypoglycaemic episodes, and the one that occurred the previous night has prompted Amanda and Steve to bring her to see you. Steve had to get up at about 3.00 a.m. to void and heard some noises from Felicity's room. He went in and found her tossing, turning and mumbling. Her bedclothes were soaked.

Amanda measured Felicity's BGL as 2.2 mmol/L and managed to get her to drink some Lucozade. Later, when Felicity was able to talk, she ate some biscuits. Her BGL rose to 12.6 mmol/L and everyone went back to bed. This is the first hypoglycaemic episode that Felicity has not been able to manage herself. The whole family is very worried because there does not seem to be any reason for this severe hypo or the run of hypos Felicity has been having.

What conditions associated with type 1 diabetes should you consider in Felicity, and what tests should you perform?

There are four autoimmune endocrine conditions that can predispose to hypoglycaemia:

- two relatively common – hypothyroidism and coeliac disease
- two relatively uncommon – hypoadrenalism and hypopituitarism.

Autoimmune thyroiditis

Thyroid autoantibodies are common in type 1 diabetes (up to 20%), with a higher prevalence in females, with increasing age and in those with glutamic acid decarboxylase (GAD) autoantibody (a diabetes-specific autoantibody).[6-8] Most people with thyroid autoantibodies remain euthyroid but some (2 to 5%) develop hypothyroidism and hyperthyroidism occurs in a few (1 to 2%).[7,9] Clinical or subclinical hypothyroidism can result in more frequent and more severe episodes of hypoglycaemia and can reduce linear growth.[10]

Because of the high prevalence of autoimmune thyroiditis, the Australian guidelines for type 1 diabetes recommend screening for thyroid autoantibodies (anti-TPO) as well as thyroid function (TSH) at diagnosis of type 1 diabetes.[11] Thyroid function tests (TSH) should be repeated yearly if thyroid autoantibodies are detected and at least second-yearly in all other patients with type 1 diabetes.[11]

Coeliac disease

In Australia, coeliac disease affects approximately 5% of children and adolescents with type 1 diabetes, with an incidence of about one per 100 person years.[11,12] It is more common in infants and in those with thyroid disease or who were diagnosed with type 1 diabetes at a younger age.[13]

Screening tests for coeliac disease include antiendomysial antibodies (EMA), IgA; antigliadin antibodies (AGA), either IgA or IgG; and anti-tissue transglutaminase antibody (tTgA), IgA and IgG. Because the IgA versions of these tests can give false-negative results in people who are IgA deficient (about one in 500 individuals), total IgA should also be measured and then IgG-tTgA or IgG-EMA if IgA deficiency is confirmed.[13] In patients with

TABLE. POLYGLANDULAR AUTOIMMUNE SYNDROME TYPE 2 (PAG-2)[14,15]

Features of PAG-2	Prevalence (%)
Endocrine	
Adrenal insufficiency	100
Autoimmune thyroid disease	70
Type 1 diabetes mellitus	50
Primary hypogonadism	5 to 50
Diabetes insipidus	<1
Nonendocrine	
Vitiligo	4
Alopecia, pernicious anaemia, myasthenia gravis, immune thrombocytopenic purpura, Sjögren's syndrome, rheumatoid arthritis	≤4

positive serology, small bowel biopsy is required to confirm the diagnosis by demonstrating inflammation or villus atrophy.

Coeliac disease is often asymptomatic but can lead to hypoglycaemia in people with diabetes, low bone mineral density and slower rates of growth. The Australian guidelines for type 1 diabetes recommend screening children and adolescents for coeliac disease at the time of diabetes diagnosis and rescreening those with negative results at least once in the five years thereafter.[11] All adults with newly diagnosed type 1 diabetes and those with type 1 diabetes who have not previously been screened should also be tested.[11]

Hypoadrenalism

There are two polyglandular autoimmune syndromes associated with type 1 diabetes:[14,15]

- the type 1 syndrome, which can cause hypoadrenalism and hypopituitarism – as this is extremely rare, it will not be discussed further here
- the type 2 syndrome, which is less rare but still uncommon, and where hypoadrenalism is the main feature.

The type 2 syndrome is characterised by primary adrenal failure (autoimmune Addison's disease) in combination with autoimmune thyroid disease and/or type 1 diabetes, primary hypogonadism and other autoimmune conditions that are less common (Table).

Hypoadrenalism (and hypopituitarism) can be the cause of more frequent and more severe apparently unexplained hypoglycaemia, as is occurring in Felicity. In Felicity's case, clinical features of hypothyroidism, coeliac disease and hypoadrenalism should be sought and tested for (thyroid function tests, thyroid autoantibodies and coeliac antibodies, and morning cortisol or short Synacthen test if clinically indicated). An endocrinologist could also provide useful advice.

The case continued

The results of Felicity's tests for hypothyroidism and coeliac disease are as follows:

- *thyroid function tests: TSH, 2.9 mIU/L (normal range 0.5 to 4.0 mIU/L) and free T4, 14 pmol/L (normal range 10 to 25 pmol/L)*
- *thyroid autoantibodies: anti-TPO, 115 IU/L (range <50 IU/L)*
- *coeliac antibodies: IgA-EMA, strongly positive.*

How do you interpret these results and is any intervention indicated?

Felicity now potentially has three autoimmune endocrine problems:

- type 1 diabetes
- the early stages of autoimmune thyroid disease (positive thyroid autoantibodies)
- probable coeliac disease (positive endomysial antibodies).

The autoimmune thyroid disease is not causing biochemical hypothyroidism but may well cause problems in the future, either as subclinical hypothyroidism (normal free T4 levels but increased TSH levels), which would predispose Felicity to hypoglycaemia and reduced growth, or with the symptoms and signs of clinical hypothyroidism.

Felicity almost certainly has coeliac disease as the IgA endomysial antibody is highly specific for coeliac disease (false positive results < 3%).[13,16] However, it is recommended that small bowel biopsy and histology be performed to confirm the diagnosis. If the coeliac antibody results are positive and the biopsy negative then it may be that the biopsy or the pathologist has missed abnormal mucosal areas or that the person has been on a gluten-free diet beforehand. Reviewing the histology and, if it is confirmed to be normal, repeating serology and biopsy after several weeks on a gluten- rich diet may confirm the diagnosis.

Family members of a person with coeliac disease may also be affected by autoimmune endocrine diseases. If coeliac disease is confirmed in Felicity, her first-degree relatives (parents and siblings) should be screened by coeliac antibody testing. As both Amanda and Felicity have autoimmune thyroid disease, family members should also be screened for thyroid autoantibodies, and the possibility that they may in the future develop serological, biochemical or clinical evidence of thyroid disease should be kept in mind.

It is also worth remembering that Amanda has two of the common autoimmune endocrine diseases in polyglandular autoimmune syndrome type 2 and may well develop others in the future, particularly adrenal insufficiency.

The case continued

Felicity's biopsy confirmed mild villous atrophy, and she and Amanda consulted a dietitian about a gluten-free diet and joined the Coeliac Society (www.coeliacsociety.com.au). The whole family adopted a gluten-free diet and Felicity grew normally through adolescence. She had a few problems with her diabetes over the years but no episodes requiring hospitalisation.

AUTOIMMUNE ENDOCRINE CONDITIONS AND PREGNANCY

The case continued

Felicity is now 24 years old, married, taking the oral contraceptive pill and wants to become pregnant.

What advice should you give Felicity, and what monitoring is indicated?

Felicity's three autoimmune problems could complicate the course of her pregnancy.

Preconception

Type 1 diabetes

Felicity's glycaemia should be well controlled (ideally HbA_{1c} below 6%, i.e. within normal limits) before she stops contraception so that her baby is not exposed to hyperglycaemia in the first weeks of gestation.[11] If she waits until she knows she is pregnant before achieving good glycaemic control, her baby may have had several weeks of exposure to hyperglycaemia already and will probably have several more as she tries to achieve blood glucose targets.

Felicity would benefit from referral to a multidisciplinary team that includes diabetes and obstetric medical, nursing and allied health specialists to discuss preconception care and care during the pregnancy.[11]

Autoimmune thyroid disease

Subclinical or clinical hypothyroidism could reduce Felicity's fertility and increase the risk of miscarriage.[17] Her thyroid function should be checked and thyroxine replaced if needed. Felicity should take iodine before and during pregnancy.

Coeliac disease

If Felicity has been on a gluten-free diet then her endomysial antibodies should be negative, suggesting that her small bowel is no longer inflamed and that intestinal absorption will be normal. Her iron, folate, vitamin B_{12} and vitamin D levels should be checked, and she should have the usual recommended nutritional supplements.[18] A dietitian experienced in both pregnancy and coeliac disease could advise Felicity on any changes that might be necessary to her current diet and could maintain contact with her during the pregnancy.

Intrapartum

Type 1 diabetes

Hyperglycaemia early in pregnancy increases the rate of congenital malformations, miscarriage and perinatal mortality. Hypoglycaemia is more common early in pregnancy than at other times, and insulin doses may need to be decreased.[19] Ketogenesis is accelerated throughout pregnancy, increasing the risk of ketoacidosis.[19]

With the increased insulin resistance associated with pregnancy, Felicity's insulin requirements can be expected to increase in the second half of her pregnancy, particularly in the third trimester. However, glycaemic control usually becomes easier as the pregnancy continues. Pregnancy affects red cell survival and can lower the HbA_{1c} levels at any prevailing level of glycaemia. Because the HbA_{1c} level at any one time reflects the average glycaemia over the preceding six weeks or so, it is important to monitor both BGL values and HbA_{1c} levels to monitor trends over time.

Autoimmune thyroid disease

Thyroxine requirements increase during pregnancy and may precipitate the onset of subclinical or clinical hypothyroidism in a woman predisposed to autoimmune thyroid disease (like Felicity) or require the use of increased thyroid hormone replacement therapy. Hypothyroidism increases the risk of serious problems (including anaemia, pre-eclamptic toxaemia and placental abruption).[17]

Coeliac disease

The requirements for a range of nutrients increase during pregnancy so Felicity should continue to liaise with her dietitian.

Postpartum

Type 1 diabetes

Immediately postpartum there is a dramatic decrease in insulin resistance and insulin requirements as the placenta is delivered, and there is a risk of hypoglycaemia then and in the few weeks after delivery. Postpartum, Felicity will have the problems of coping with the demands of her first-born baby, her diabetes, her coeliac disease and more, and would benefit from practical and moral support.

Autoimmune thyroid disease

If Felicity had not been hypothyroid before or during pregnancy then she is at high risk of developing postpartum thyroiditis (as her mother Amanda did). Felicity's thyroid function should be monitored, as described earlier (see page 40).[11]

Coeliac disease

As previously noted, Felicity's life postpartum will be challenging and it may be difficult for her to go to the extra trouble of maintaining a gluten-free diet for herself and ideally for the whole family. Familial, social, psychological and health professional support could help her meet these challenges.

Other autoimmune endocrine diseases after pregnancy

Once the immunomodulatory effects of pregnancy are over, other autoimmune diseases may occur (such as other components of the polyglandular autoimmune syndrome type 2, especially adrenal insufficiency). At some stage (e.g. when a blood test is already indicated), Felicity's baby should be assessed for autoimmune endocrine diseases and a plan made to monitor the risk of these conditions (particularly coeliac disease and thyroid disease) in the future.

SUMMARY

- Type 1 diabetes is associated with two other common forms of autoimmune endocrine disease (thyroid disease and coeliac disease) and with several other less common autoimmune conditions (mainly polyglandular syndrome type 2, the main feature of which is hypoadrenalism).
- Autoimmune thyroid disease is the most common autoimmune endocrine disease associated with type 1 diabetes, occurring as either:
  - postpartum thyroiditis, which occurs in 25% of pregnant women with type 1 diabetes and has periods of hyper- and hypothyroidism or only the hyper- or hypothyroid components, with subsequent progression to permanent autoimmune hypothyroidism in some women rather than return to normal thyroid function, or
  - subclinical or classical hypothyroidism, which may occur independent of pregnancy and be associated with decreased linear growth in children with type 1 diabetes and hypoglycaemia in all people with type 1 diabetes.
- It is recommended that screening for autoimmune thyroid disease (thyroid function tests and antibodies) be performed at the time of diagnosis of diabetes and repeated yearly if antibodies are present and second-yearly if antibodies are absent.
- Coeliac disease affects approximately 5% of children with type 1 diabetes and can also occur in adults.
- Screening for coeliac antibodies is recommended at the time of diabetes diagnosis and in people with type 1 diabetes who have not previously been screened, with repeat screening for children and adolescents at least once in the subsequent five years.
- Two forms of polyglandular autoimmune syndrome are associated with type 1 diabetes: type 1, which is extremely rare, and type 2, which is more common. Type 2 has hypoadrenalism as the main feature and is associated with autoimmune thyroid disease and hypogonadism.
- Unexpected hypoglycaemia in a person with type 1 diabetes can be caused by undiagnosed hypothyroidism, coeliac disease, hypoadrenalism and, rarely, hypopituitarism.
- Pregnancy care in women with type 1 diabetes should include tight glycaemic control preconceptionally as well as during pregnancy. Associated hypothyroidism will require increased thyroxine replacement as thyroid requirements increase in pregnancy. Associated coeliac disease will require preconception and ongoing nutritional assessment and supplements as well as close adherence to a gluten-free diet.
- Although autoimmune diseases may occur or become more severe post-partum in women with or without diabetes as the immunoregulatory system recovers from suppression during pregnancy, this is particularly likely to occur in women with type 1 diabetes. MT

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References are included in the pdf version of this article available at www.medicinetoday.com.au.

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PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)
JESSICA PHILLIPS MB BS

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