Diabetes and thyroid disease: A common association with clinical consequences

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Article points

1. Hypothyroidism is the most common thyroid disorder in the adult population.
2. Epidemiological data have confirmed a shared genetic susceptibility to autoimmune thyroid and adrenal disease and type 1 diabetes.
3. The effect of hypothyroidism or hyperthyroidism on body weight may affect diabetes management and influence HbA_{1c} levels and the risks of hypoglycaemia.

Key words

- Autoimmune disorders
- Hyperthyroidism
- Hypothyroidism
- Postpartum thyroiditis
- Thyroid disease

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Both diabetes and thyroid disease are common in the general population and their coexistence in the same person by chance is not unexpected. Thyroid diseases leading to over- or under-activity of gland function may influence glycaemic control through effects on body weight and insulin action. There is also an association between type 1 diabetes and autoimmune thyroid disease, where abnormalities of the innate immune system play a central role in the pathogenesis of both. This underpins current recommendations for screening people with type 1 diabetes for thyroid disorders as part of routine clinical practice. This article briefly reviews thyroid disease before describing the evidence linking diabetes and thyroid disease and highlighting particular clinical situations such as pregnancy and post-partum thyroiditis.

Thyroid disorders are common in clinical practice and more so in people with diabetes, especially type 1 diabetes (Wu, 2000). Thyroid disease is significantly more common in females and the prevalence increases with age (Tunbridge et al, 1977).

Over 90% of cases of hyperthyroidism are due to Graves' disease, an autoimmune disorder characterised by IgG antibodies that trigger thyroid stimulating hormone (TSH) receptors on thyroid follicular cells, increasing thyroid hormone production and thyroid cell growth. Clinical features include hyperthyroidism, a diffuse goitre, and other specific features, including exophthalmos and dermopathy, which do not present in cases of hyperthyroidism not caused by Graves' disease. Graves' disease typically runs a relapsing, remitting course, unlike other causes (*Table 1*), which are either persistent or self-limiting.

A diagnosis of hyperthyroidism is confirmed with blood tests showing raised free T4 and T3 concentrations and suppression of pituitary derived TSH to undetectable levels. In around 5% of people, free T3 may be increased with normal free T4 levels consistent with T3-toxicosis. Raised titres of anti-thyroid peroxidise (TPO) antibodies – serum markers of autoimmunity – are present in 60% of cases. Sub-clinical hyperthyroidism, diagnosed by finding a suppressed TSH level in association with thyroid hormones in the laboratory reference range, is associated with a three- to five-fold increased risk of atrial fibrillation (Sawin et al, 1994).

Hypothyroidism is the most common thyroid disorder in the adult population. Most cases are autoimmune in origin (such as primary atrophic hypothyroidism or Hashimoto's thyroiditis) or iatrogenic (post-thyroidectomy or post-radioactive iodine therapy).

In Hashimoto's thyroiditis, the thyroid gland is infiltrated with immunologically activated lymphocytes that target and progressively destroy

thyroid follicular cells, eventually leading to a fall in thyroid hormone levels in the blood. People with Hashimoto's thyroiditis have antibodies to various thyroid antigens, most frequently anti-TPO, anti-thyroglobulin (anti-TG) and, to a lesser extent, TSH receptor-blocking antibodies.

The diagnosis of hypothyroidism is confirmed by finding low free T3 and T4 concentrations associated with a raised TSH level. The increased level of TSH is the pituitary gland response to insufficient thyroid hormone in the blood and is a physiological response to stimulate the ailing thyroid to correct the thyroid hormone deficiency. Anti-TPO antibodies are more commonly found in Hashimoto's thyroiditis than Graves' disease (95%), usually at a higher titre. Sub-clinical hypothyroidism is defined as a raised TSH level in association with normal thyroid hormone levels and is associated with increased cholesterol levels and possibly an increase in cardiovascular risk (Rodondi et al, 2006).

Autoimmune thyroid disease and type 1 diabetes: More than a chance association?

An association between autoimmune thyroid and adrenal disease (AITD) and type 1 diabetes was first reported by Bennett et al in 1964. Since then, epidemiological data has confirmed a shared genetic susceptibility to AITD and type 1 diabetes. Both conditions frequently occur within the same family and in the same individual.

People developing both type 1 diabetes and AITD are considered to have an autoimmune polyglandular syndrome type 3 variant. Villano et al (2009) demonstrated a strong shared genetic susceptibility to type 1 diabetes and AITD, with most shared genes involved in immune regulation, suggesting that immune dysregulation plays an important role in increasing susceptibility to type 1 diabetes and AITD.

The significance of these associations can be readily appreciated in a cross-sectional study in which 197 people with recent-onset type 1 diabetes had blood taken to measure the prevalence and co-occurrence of organ-specific auto-antibodies linked with thyroid disease, coeliac disease, Addison's disease and pernicious anaemia (Jaeger et al, 2001). Antibody levels were compared with 882 first-degree relatives and 150 healthy controls. Thyroid and coeliac antibodies were detected more frequently both in people with recent-onset type 1 diabetes and, to a lesser degree, in first-degree relatives ($P<0.05$) compared with healthy participants.

Epidemiology of autoimmune thyroid disease and diabetes

A number of studies have investigated links between diabetes and thyroid disease. In a study of 1310 adults with diabetes in Scotland the overall prevalence of thyroid disease was 13.4% (Perros et al, 1995). The highest prevalence was 31.4% in females with type 1 diabetes and lowest (6.9%) was seen in males with type 2 diabetes. New thyroid disease was diagnosed in 6.8% of the population screened; the most common diagnosis was subclinical hypothyroidism (4.8%), followed by hypothyroidism (0.9%), hyperthyroidism (0.5%), and subclinical hyperthyroidism (0.5%). Female participants with type 1 diabetes had the highest annual risk of developing thyroid disease (12.3%), but all groups of participants had a higher incidence of thyroid dysfunction compared with the general population (Perros et al, 1995).

To investigate thyroid autoimmunity in children and adolescents with type 1 diabetes, thyroid-associated antibodies were measured in 7097

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1. In Hashimoto's thyroiditis, the thyroid gland is infiltrated with immunologically activated lymphocytes that target and progressively destroy thyroid follicular cells, eventually leading to a fall in thyroid hormone levels in the blood.
2. An association between autoimmune thyroid and adrenal disease and type 1 diabetes was first reported by Bennett et al in 1964.

Box 1. Causes of hyperthyroidism and hypothyroidism.

Other causes of hyperthyroidism (Townsend et al, 2008)

- Toxic multi-nodular goitre.
- Toxic adenoma.
- Sub-acute (deQuervain's) thyroiditis.
- Silent thyroiditis.
- Inherited autosomal dominant hyperthyroidism.
- Post-partum thyroiditis.
- Iodine induced hyperthyroidism.
- Hyperthyroidism due to thyroid stimulating hormone or thyroid stimulating hormone receptor agonists.
- Drugs (for example, amiodarone, lithium, contrast agents etc.)
- Thyrotoxicosis due to non-thyroid sources of thyroid hormone (thyrotoxicosis factitia, ectopic thyroid tissue)

Causes of hypothyroidism

- Autoimmune thyroid and adrenal disease (Hashimoto's thyroiditis, Graves' disease).
- Secondary to radioactive iodine therapy.
- Post-thyroid surgery.
- Secondary hypothyroidism (due to pituitary or hypothalamic disorders).
- Drugs (for example, amiodarone, lithium, para-aminosalicylic acid, phenylbutazone etc.).
- Inherited defects in thyroid hormone synthesis (defects in thyroid peroxidase and thyroglobulin production).
- Thyroid hormone resistance.

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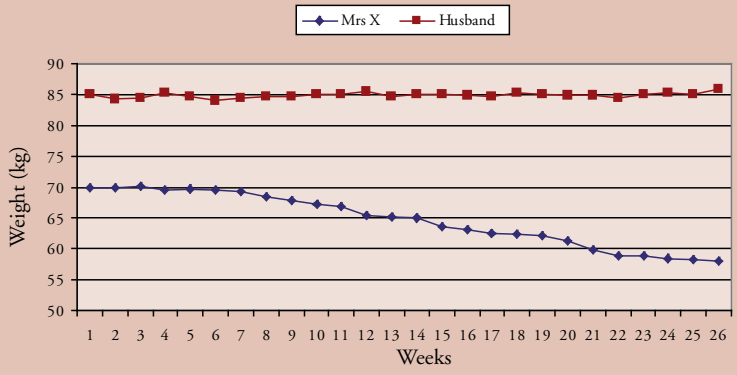
1. A study revealed that thyroid autoimmunity is particularly common in girls with type 1 diabetes during the second decade of life and may be associated with elevated TSH levels, indicating possible evolving subclinical hypothyroidism.
2. hyperthyroidism aggravates glucose intolerance by multiple mechanisms including increased hexose intestinal absorption, decreased responsiveness to insulin, and increased glucose production.

people in Germany and Austria (Kordonouri et al, 2002). Thyroid antibody levels were raised on at least one occasion in over 1 in 5 (21.6%) participants. Those with raised thyroid antibodies were older (P<0.001), had longer duration of diabetes (P<0.001), and had developed diabetes later in life (P<0.001) than those without antibodies. Two thirds of participants with positive antibodies were girls. The prevalence of significant antibody titres increased with age with the highest prevalence in the 15–20 year age group (anti-TPO: 16.9%, P<0.001; anti-TG: 12.8%, P<0.001). Thyroid function was altered in people with raised antibody levels with higher TSH levels (3.34 mU/L) compared with controls (1.84 mU/L) (P<0.001). Even higher TSH levels were observed in those with both anti-TPO and anti-TG (4.55 mU/L). Hence, the study revealed that thyroid autoimmunity is particularly common in girls with type 1 diabetes during the second decade of life and may be associated with elevated TSH levels, indicating possible evolving subclinical hypothyroidism (Kordonouri et al, 2002).

Box 2. Case example

A 64-year-old woman (Mrs X) with type 2 diabetes lived with her 68-year-old husband. For some years she had kept weekly records of her and her husband's weight (see below).



Her medication was: Metformin 1 g twice-daily; Simvastain 40 mg at night-time; Ramipril 10 mg once-daily; Gliclazide 80 mg twice-daily; aspirin 75 mg once-daily.

Although not actively trying to lose weight, Mrs X was pleased with this weight loss since her glycaemic control had improved with home blood glucose readings falling as low as 3.5 mmol/L on waking. She had, however, experienced episodes of hypoglycaemia and also some palpitations on exercise. Her HbA_{1c} level had fallen from 8.6% (70 mmol/mol) to 6.5% (48 mmol/mol). Thyroid function tests revealed primary hyperthyroidism (free T4: 52 nmol/L [healthy range: 12–24 nmol/L], free T3: 18.7 nmol/L [healthy range: 3.6–7 nmol/L] thyroid stimulating hormone <0.01 mU/L [healthy range: 0.5–4 mU/L]. She was commenced on carbimazole and referred for radioactive iodine therapy. Her gliclazide medication was reduced temporarily to lessen the risk of hypoglycaemia.

Finally, in a longitudinal study, 58 participants (32 females) enrolled in the Diabetes Control and Complications Trial (DCCT) were monitored for the incidence of thyroid dysfunction over 18 years of follow-up (Umpierrez et al, 2003). Eighteen had hypothyroidism and one experienced transient hyperthyroidism. The mean age of diagnosis was 19±2 years for type 1 diabetes and 29±3 years for hypothyroidism. Hypothyroidism was more common in women (41%) than in men (19%) and thyroid antibody positive participants were almost 18 times more likely to develop hypothyroidism compared with those who were thyroid antibody negative.

Clinical consequences

Thyroid disease may impact on diabetes in a number of ways. First, the effect of hypothyroidism or hyperthyroidism on body weight may affect diabetes management and influence HbA_{1c} levels and the risks of hypoglycaemia in either type 1 or type 2 diabetes (see *Box 2* for an example of type 2 diabetes).

Second, abnormalities of thyroid hormone levels may influence insulin action. Manifest hypothyroidism decreases insulin sensitivity and increases glucose stimulated insulin release in healthy people and people with type 2 diabetes. Insulin clearance is also reduced (Mohn et al, 2002). These changes, which increase the risk of hypoglycaemia, are reversible with thyroxine replacement, but adjustment of diabetes therapy may be required to maintain glycaemic control as thyroxine doses are optimised. Even sub-clinical hypothyroidism increases demand on pancreatic beta-cells (Cáp, 2009). In contrast, hyperthyroidism aggravates glucose intolerance by multiple mechanisms, including increased hexose intestinal absorption, decreased responsiveness to insulin and increased glucose production.

Conflicting results are obtained when circulating insulin levels are measured in hyperthyroidism. The role of glucagon and alpha-cell sensitivity is unclear. Diabetes may influence the assessment of hyperthyroidism by falsely decreasing the blood levels of T4 and T3 during severely uncontrolled hyperglycaemia (Mouradian and Abourizk, 1983).

Third, clinicians need to be aware of the increased risk of post-partum thyroiditis (PPT)

in women with type 1 diabetes. PPT is an autoimmune mediated disturbance of thyroid function in the 12-month post-partum period characterised by the occurrence of either transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by transient hypothyroidism (*Figure 1*).

In 80% of women, thyroid function returns to normal at 1 year, but hypothyroidism persists in approximately 20% (Alvarez-Marfany et al, 1994; Othman et al, 1990). The prevalence of PPT ranges between 1.1% and 16.7% (mean prevalence rate of 7.2%) (Stagnaro-Green, 2002). PPT risk is predicted by positive anti-TPO antibodies in the first trimester and it commonly recurs in future pregnancies.

In a long-term prospective study of PPT, 41 women with type 1 diabetes had regular thyroid function tests during the second and third trimester of pregnancy and at 6 weeks, 3, 6, 9 and 12 months postpartum. The incidence of PPT was 25%, suggesting a 3-fold increase compared with a similar study in a non-diabetic population. Forty-three percent of these women required treatment for thyroid dysfunction (Alvarez-Marfany et al, 1994).

The American Diabetes Association (ADA, 2009) suggest that those at risk of PPT include those with a previous history of autoimmune thyroid disease, or positive thyroid antibodies in the first trimester and those with a family history of thyroid disease.

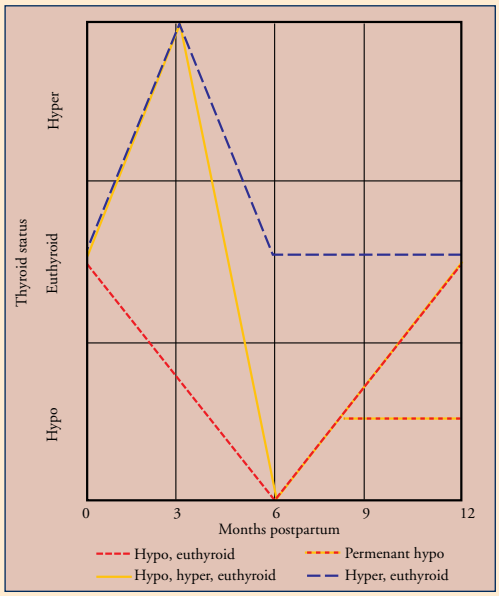


Figure 1. The time course and pattern of thyroid function tests in postpartum thyroiditis.

Finally, there are data suggesting an increased risk of adverse cardiovascular and renal outcomes in people with type 2 diabetes and sub-clinical hypothyroidism (Chen et al, 2007). Overt and sub-clinical hypothyroidism is associated with increased total and LDL cholesterol levels (Canaris et al, 2000). Optimal thyroxine replacement lowers serum cholesterol, and thyroid function should be carefully monitored in people with known diabetes and dyslipidaemia. In those with sub-clinical hypothyroidism, treatment with thyroxine should be initiated, particularly if the TSH is persistently over 10 mU/L since a decrease in serum cholesterol may be anticipated (Meier et al, 2001).

Thyroid disease screening in diabetes

Current ADA (2009) guidelines recommend that people with type 1 diabetes should be screened for thyroid antibodies at diagnosis. Once metabolic control of diabetes has been achieved, thyroid function (free T4 and TSH) should be measured, and then re-checked as part of routine care every 1–2 years, or if the person develops features of thyroid disease. Thyroid antibodies should also be measured in women with type 1 diabetes during the first trimester of pregnancy and their thyroid function tests should be monitored every 3–4 months for the first year postpartum. Thyroid function should also be checked if there are unexplained changes in weight of any people with diabetes and as part of the investigations into an increased frequency of hypoglycaemia that could be related to evolving hypothyroidism.

Conclusion

People with type 1 diabetes are more likely to develop thyroid disease and coeliac disease due to the similar autoimmune pathologies of these conditions. Healthcare professionals should be aware of the clinical consequences of thyroid disease in diabetes, including the impact on body weight, hypoglycaemia, PPT in women and adverse cardiovascular and renal outcomes. Screening for thyroid disease in people with diabetes is an important part of their care. ■

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