



Screening patients with type 1 diabetes and hypothyroidism for related autoimmune diseases

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Abstract

This review critically discusses the importance of screening patients with type 1 diabetes and hypothyroidism for related autoimmune diseases. It provides insights into the prevalence of thyroid disorders and diabetes mellitus, as well as the connection between T1D and hypothyroidism. The review also highlights the benefits of early detection and the implications for health policy, practice, research, and medical education. Overall, this article provides valuable information for healthcare providers on how to screen patients for related autoimmune diseases and provide them with the best possible care.

Keywords: Hypothyroidism, Type 1 diabetes mellitus, Autoimmune diseases, Autoimmune polyendocrine syndrome, Screening tests, Autoimmune endocrine diseases, Non-endocrine autoimmune disorders

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Introduction

Thyroid disorders and diabetes mellitus are among the most common endocrine diseases worldwide. In Europe and the United States, the prevalence of thyroid disorders in adults is 6.6%, with higher rates among female than males (1). Hypothyroidism is one of the most common endocrine diseases. The leading causes of this condition are iodine deficiency and an autoimmune disease known as Hashimoto's disease. Hypothyroidism is nearly ten times more common in women than in men. The prevalence of hypothyroidism in the general population varies between studies, ranging from 0.3 to 3.7% in America and 0.2 to 5.3% in Europe (2).

The number of people with type 1 diabetes (T1D) is rising worldwide, both in incidence and prevalence, with an average annual growth rate of around 2–3% per year. According to United States data, the average yearly incidence from 2001 to 2015 was about 22.9 cases per 100 000 people for those under 65 years old. Similar incidences were reported from other regions. The most noticeable increases in new cases of T1D were among children under 15 years old, especially those under five (3).

Approximately 25% of children with T1D also have autoimmune hypothyroidism (4). As a result, patients with T1D tend to develop hypothyroidism earlier than the general population. Children with autoimmune diseases such as hypothyroidism and T1D are at risk of

developing other autoimmune conditions. Early screening is important to help with early diagnosis (5).

This study aims to explore the relationship between hypothyroidism and T1D and their association with other autoimmune diseases. Furthermore, it will investigate the screening tests used for these types of patients.

Review of literature

Prevalence of thyroid dysfunction (TD) in patients with T1D

Type 1 diabetes is an autoimmune disease that damages the beta cells of the pancreas, leading to a severe decrease in insulin production. This disease is related to autoimmune thyroid disorders due to their similar pathophysiology. Genetic factors can cause T1D and thyroid disorders to occur simultaneously (6). The risk of autoimmune thyroid diseases is higher in adults with T1D (7).

Approximately 17 to 30% of adults with T1D have autoimmune thyroid dysfunction (AITD). Patients with T1D are at risk for both types of thyroid disorders: hypothyroidism (Hashimoto's) and hyperthyroidism (Graves's disease) (7). These disorders tend to occur earlier in life in patients with T1D compared to the general population. In children with T1D and AITD, the onset of thyroid disorder symptoms is more aggressive and can result in poor glucose control in diabetes (8).

Over a period of 18 years, patients with T1D who tested positive for thyroid peroxidase (TPO) antibodies had an

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■ Implication for health policy/practice/research/medical education

This study suggests that type 1 diabetes and autoimmune hypothyroidism patients should be screened for other autoimmune endocrine diseases since these are part of an autoimmune polyglandular syndrome (APS). Additionally, a screening test is recommended for other coexisted non-endocrine autoimmune disorders.

18 times greater chance of developing hypothyroidism than patients with T1D who tested negative for TPO antibodies. The onset of thyroid disorders is related to the duration of diabetes (9).

The relationship between T1D and AITD

Type 1 diabetes and AITD are part of the autoimmune polyglandular syndrome type 3 variant (APS3). However, T1D and AITD can also be classified as juvenile APS type 1 and adult APS type 2. In these two syndromes, T1D and AITD are not among the main disorders (10).

The prevalence of APS3 is approximately 1 in 20 000 people. The risk of APS3 is three times greater in women than in men. The occurrence of APS3 reaches its highest point between the ages of 20 and 60 years, with the highest rates peak between 30s to 40s (11).

When autoimmune hypothyroidism and T1D occur simultaneously, we can see an increase in the risk of hypoglycemia because the need for insulin decreases and insulin sensitivity increases.

In some cases, antibodies may react with multiple glands. While antibodies often appear before the onset of clinical disease, anti-thyroid antibodies can exist for many years without leading to illness. To diagnose APS3, physicians measure levels of organ-specific antibodies in the blood and perform functional tests. These tests include checking baseline levels of hormones such as thyroid function tests, sex hormones (testosterone and estradiol), fasting blood glucose (FBS), and cortisol. If adrenal antibodies are present, an adrenocorticotrophic hormone stimulation test may also be done. Other useful measurements include serum levels of sodium, potassium, calcium, and blood cell count (10).

The influence of hypothyroidism on metabolic processes and its effect on the regulation of blood glucose levels

The symptoms of hypothyroidism can include a delay in the absorption of glucose in the peripheral tissues, in the intestine, and a decrease in gluconeogenesis in the liver and muscles, as well as a normal or decreased glucose output in the liver (12). The half-life of insulin is increased, and its secretion rate can be normal or increased (13).

It has been shown that muscle cells and adipocytes respond less to insulin in hypothyroid mice (14). In hypothyroidism, glucose consumption in peripheral tissues, glucose oxidation rate, and glycogen synthesis

decrease. Insulin resistance occurs in patients with overt and subclinical hypothyroidism because insulin cannot cause glucose consumption in muscles (15,16).

A previous study reported a positive relationship between overt and subclinical hypothyroidism and increased FBS levels (17). Several studies have shown a relationship between increased insulin levels and decreased clearance in hypothyroidism patients (18). Increased free fatty acids can cause insulin resistance in hypothyroidism patients, impaired glucose transporter type 4 (GLUT4) function, and inappropriate leptin function in the hypothalamus (19).

The development of insulin resistance in hypothyroidism may be due to several factors, including disrupted leptin function in the hypothalamus, impaired translocation of GLUT4, and increased free fatty acids. Research has shown that insulin-stimulated glucose transport is reduced in monocytes isolated from patients with subclinical and overt hypothyroidism. This suggests that similar changes may occur in peripheral tissues due to the impaired movement of GLUT4 to the cell surface (19).

In patients with hypothyroidism, levothyroxine treatment has been shown to increase glucose-dependent insulin secretion by beta cells (20). The need for insulin in diabetic patients with hypothyroidism decreases due to reduced insulin clearance (21). Hypoglycemic symptoms can occur in patients with diabetes and hypothyroidism when they do not reduce their dose of exogenous insulin despite a decrease in their need for it (22).

Screening of TD in pregnant patients with DIM

The American Association of Clinical Endocrinologists, the Endocrine Society, the British Thyroid Association (BTA), and the American Diabetes Association (ADA) recommend that women with T1D or other autoimmune diseases be screened for TD.

Women with T1D planning a pregnancy or in the early stages of pregnancy should have their thyroid stimulation hormone (TSH) and TPO antibody (Ab) levels evaluated. Screening should be repeated during the first trimester if thyroid function is normal. If TPO Abs are positive, however, serum TSH is normal during pregnancy, thyroid function should be rechecked at 3, 6, and 12 months after delivery. Additionally, patients with T1D should be screened for postpartum thyroiditis at 3 and 6 months postpartum (23).

Evaluating patients with T1D for TD

Thyroid dysfunction is a common disease in people with T1D, and its prevalence increases with age. The onset of TD can cause poor blood glucose control due to subclinical or overt hypothyroidism in T1D, leading to overt hypoglycemic symptoms.

Screening for TD in T1D patients can be justified for several reasons; 1) T1D and TD are often related. 2) Clinical and laboratory diagnostic methods are readily

available and easily performed. 3) Delayed or missed diagnosis of TD can worsen the prognosis for T1D patients. 4) Effective treatments exist for both TD and T1D. As a result, screening for TD in T1D patients is cost-effective.

Several medical organizations, like the American Association of Clinical Endocrinologists, and the International Society for Pediatric and Adolescent Diabetes, recommend screening for TD in children, adolescents, and adults with T1D.

The International Society for Pediatric and Adolescent Diabetes states that thyroid antibody and thyroid function tests should be performed when diagnosed with T1D. These tests should be repeated when the patient shows symptoms of thyroid disease. Thyroid tests should be checked annually. As a result, all patients with T1D, especially those with positive TPO abs, must perform an annual thyroid function test, which is performed by measuring TSH, to detect asymptomatic TD in patients. Additionally, to lower the chances of developing high cholesterol and heart disease caused by fatty deposits in patients with T1D and low thyroid function, treatment with levothyroxine should be initiated (24,25).

To ensure proper thyroid function, it is important to have regular check-ups. If TPO antibodies are initially negative, tests should be done every one to two years. However, if TPO antibodies are present or if there are signs of thyroid problems such as an enlarged thyroid gland (goiter), abnormal growth in children, or unexpected changes in blood sugar levels, testing should be done more often, up to every six months (26).

Thyroid dysfunction screening should be done by thyroid antibodies and serum TSH because these are the most sensitive methods for evaluating autoimmune diseases and TD (26). To rule out or confirm any abnormal findings, several lab tests should be performed over a period of three to six months. Follow-up tests taken with T4 can differentiate between subclinical hypothyroidism and overt hypothyroidism (26).

These suggestions highlight the significance of testing for TD in individuals with T1D (26,27).

To assess the likelihood of T1D coexisting or developing in AITD patients, particularly in younger individuals or those with a family history of T1D, physicians can measure fasting glucose, hemoglobin A1C (HbA1c), islet cell Abs, and glutamic acid decarboxylase Abs at the time of AITD diagnosis.

Tests suggested in patients with both T1D and autoimmune thyroid disease

If T1D and AITD coexist, it is recommended to conduct genetic studies and serological screenings in first-degree relatives to check for the presence of autoimmune polyendocrine syndrome (28). Since people with T1D and autoimmune thyroid disease, as well as their family members, have a higher chance of developing other

autoimmune diseases, it is recommended to test for glandular autoantibodies and perform blood tests in all APS3 patients and their close relatives (29).

It is also recommended to perform serological screenings for common nonendocrine autoimmune disorders associated with autoimmune polyendocrine syndrome, such as Sjögren's syndrome, pernicious anemia, autoimmune gastritis, and celiac disease. Identifying MHC HLA class II DR/DQ antigens and testing for PTPN22 and CTLA-4 gene variations can help differentiate between patients with autoimmune diseases affecting multiple glands (polyglandular) and those affecting only one gland (mono-glandular) (5,30).

Conclusion

Autoimmune diseases are a large group of conditions that include T1D and autoimmune hypothyroidism. These two diseases are part of the autoimmune polyendocrine syndrome. Screening tests should be performed for the other and related endocrine diseases when one of these diseases is diagnosed. Screening tests help identify affected individuals more quickly and reduce the disease burden in society. Due to the genetic connections between autoimmune diseases, screening for other autoimmune diseases is also recommended when T1D and autoimmune hypothyroidism are diagnosed. However, more studies are needed to understand the potential benefits of screening for non-endocrine autoimmune diseases such as Sjogren syndrome and celiac disease in patients with T1D and autoimmune hypothyroidism.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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