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Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association for the management of thyroid dysfunction in type 1 and type 2 diabetes

Zalecenia Polskiego Towarzystwa Endokrynologicznego oraz Polskiego Towarzystwa Diabetologicznego dotyczące diagnostyki i leczenia zaburzeń funkcji tarczycy w cukrzycy typu 1 i 2

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Abstract

Thyroid disorders are more frequently observed in diabetic patients. These conditions have been shown to be mainly of autoimmune origin and all of them may lead to hormonal imbalance. Especially strong links exist between autoimmune thyroid diseases (AITD) and type 1 diabetes. Importantly, both hypothyroidism and hyperthyroidism can adversely affect metabolic control of diabetes. These recommendations propose diagnostic and therapeutic algorithms for thyroid dysfunction in diabetic patients. **(Endokrynol Pol 2013; 64 (1): 73–77)**

Key words: *thyroid diseases, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, type 2 diabetes mellitus, pregnancy in diabetics*

Streszczenie

Zaburzenia czynności tarczycy dotyczą znacznej części populacji osób chorych na cukrzycę. Najczęściej są to zaburzenia o podłożu autoimmunologicznym, częściej współistniejące z cukrzycą typu 1. Zarówno niedoczynność, jak i nadczynność tarczycy pogarszają wyrównanie metaboliczne pacjentów z cukrzycą. Celem zaleceń było zaproponowanie algorytmu diagnostyczno-terapeutycznego chorób tarczycy u pacjentów z cukrzycą. **(Endokrynol Pol 2013; 64 (1): 73–77)**

Słowa kluczowe: *choroby tarczycy, niedoczynność tarczycy, nadczynność tarczycy, cukrzyca typu 1, cukrzyca typu 2, cukrzyca przedciążowa*

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Introduction

Thyroid disorders can be found in approximately 7% of the adult population [1]. Simultaneously, however, the condition is diagnosed in as much as 11% to 30% of patients with type 1 or 2 diabetes mellitus, predominantly females [2–4]. About 15% of type 2 diabetic patients suffer from overt hypothyroidism; additionally, a further 10% present subclinical hypothyroidism [5]. On the other hand, approx. 3.5% of type 2 diabetic patients are affected by overt hyperthyroidism, whereas 3% of that population are diagnosed with subclinical hyperthyroidism [5].

Thyroid dysfunction co-occurs more often with type 1 diabetes, and can affect as many as 30% of the patients. [6]. Commonest among them are autoimmune disorders (Hashimoto's thyroiditis and Graves' disease) [7].

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6–10% of type 1 diabetic patients are also diagnosed with hyperthyroidism in the course of Graves' disease.

Hypothyroidism is found in 17% of pregnant women with type 1diabetes [8]. Also, postpartum thyroiditis is observed three times more frequently in type 1 diabetic patients [9].

Diabetes mellitus is also an important risk factor for cardiovascular disease. Both hypothyroidism and hyperthyroidism adversely affect the metabolic control of diabetes. Moreover, subclinical, as well as overt hypo- and hyperthyroidism, irrespective of the concomitant diabetes, can negatively affect the cardiovascular system [10]. As a result, diabetic patients suffering from thyroid disorders constitute a group with a particularly high risk of cardiovascular disease.

The aim of this paper was to summarise the current state of knowledge on diabetes and coexisting thyroid disorders, to propose an algorithm of assessing thyroid function in diabetes mellitus patients, and to offer recommendations for the management of thyroid dysfunction in the aforementioned group.

Influence of thyroid hormones on carbohydrate metabolism

Thyroid hormones tend to increase the level of liver gluconeogenesis and glycogenolysis, as well as elevate lactate synthesis in muscle and fat tissue (Cori cycle). Additionally, liver gluconeogenesis is facilitated by stimulation of proteolysis in muscles, which leads to an increased amino acid supply to the liver. Thyroid hormones impact the number of GLUT2 transmembrane glucose transporters in hepatocytes, which also increases the load of glucose to the liver. Furthermore, elevated lipolysis during fasting causes an increase in the level of free fatty acids, also stimulating liver gluconeogenesis [11].

In hyperthyroidism, endogenous gluconeogenesis is increased and the suppressive influence of insulin on gluconeogenesis is significantly impaired. On the other hand, the increase in blood supply to tissues, including skeletal muscles, enhances glucose uptake. Hyperglycaemia in hyperthyroidism is also connected with increased intestinal glucose uptake, due to the enhanced activity of the SGLT1 Na+/glucose co-transporter in enterocytes.

Hyperthyroidism entails a decreased insulin half-life, probably as a result of increased insulin degradation and increased release of biologically inactive precursors of insulin. Additionally, a decrease in the C-peptide to proinsulin ratio has been noted, suggesting proinsulin metabolism disorders. The deterioration in the metabolic control of diabetes in hyperthyroidism could also be connected with an increase in the concentration and activity of hormones antagonistic to insulin — glucagon and catecholamines.

A reduction of both glycogenolysis in muscles and liver and gluconeogenesis in liver, as well as a decrease of both basal insulin secretion and intestinal glucose absorption, can be observed in hypothyroidism. Consequently, the condition increases the risk of recurrent hypoglycaemia. Both overt and subclinical hypothyroidism entail an increased insulin resistance connected with impaired glucose uptake in peripheral tissues.

It has been demonstrated that levothyroxine treatment normalises fasting insulinaemia and increases insulin sensitivity, without impacting upon glycaemia. It also positively influences cardiovascular disease risk factors, such as lipid profile, diastolic blood pressure, and waist-hip ratio.

Influence of diabetes mellitus on thyroid hormones

Diabetic patients have been demonstrated to have a lower peak night TSH secretion, and an impaired TSH response to TRH stimulation. Patients with poor metabolic control (HbA_{1c} > 10%) have presented inhibition of type 1 deiodinase activity, and as a result, decreased T4 to T3 conversion, lower T3 serum levels, and elevated rT3 concentration, which can be explained as the body's defence mechanism against increased tissue catabolism and against decreased tissue oxygen consumption [12].

Influence of selected drugs on thyroid hormones

In terms of the hormonal diagnostics of thyroid disorders, it should be borne in mind that other clinical conditions and administered drugs influence the concentration of TSH and thyroid hormones [13]. Antidiabetic medications can also impact the hypothalamic–pituitary–thyroid axis.

Studies show that metformin undergoes minimal biotransformation and is transported as an organic cation in a form not bound with proteins. It has been shown in an animal model that in this form it can cross the brain-blood barrier and its concentration in the hypothalamus and in the pituitary gland corresponds to its serum concentration [14]. In patients with type 2 diabetes and hypothyroidism, both treated and not treated with levothyroxine, a significant decrease of TSH without change of fT_4 has been observed after one year of treatment with metformin. A similar reaction has not been noted in euthyroid diabetic patients treated with metformin [15].

Several reports also indicate that sulfonylurea derivatives can inhibit the synthesis and secretion of thyroid hormones, as well as displace them from the binding with globulin (TBG) and/or thyroxine-binding prealbumin (transthyretin) [13]. However, studies conducted with various sulfonylureas have so far not confirmed that these drugs have a clinically significant influence on thyroid function [16].

As a result, when interpreting laboratory tests for thyroid function in patients on anti-diabetic medications, the potential influence of metformin should be taken into account. Currently, however, there are no grounds to formulate separate monitoring and treatment guidelines in patients treated with oral anti-diabetic medications. Until now there have been no clear indications regarding screening tests for thyroid disorders in diabetic patients. Both the choice of tests and their frequency remain a matter of debate.

Choice of diagnostic tests for the evaluation of thyroid function

Most clinical recommendations suggest measuring levels of TSH and anti-thyroid antibodies when diabetes is newly diagnosed. Patient monitoring is based on controlling the TSH level. A correct TSH concentration has a high predictive value, and constitutes the basis for excluding potential thyroid disorders. In certain clinical situations, assessing just the TSH level may not be sufficient to evaluate hormonal function correctly, e.g. when the hypothalamic-pituitary-thyroid axis is disrupted, during the monitoring of hyperthyroidism treatment, and during pregnancy. This also pertains to acute diabetic complications — diabetic ketoacidosis, hyperglycaemic hyperosmolar state, as well as recurrent and acute episodes of hypoglycaemia. In such situations, in order to evaluate thyroid hormonal function correctly, measuring both TSH and fT_4 during and after achieving metabolic control is recommended. Detecting an abnormal glycaemic profile in hyperthyroidism may indicate an elevated risk of developing diabetes in the future. Therefore, an oral glucose tolerance test should be performed in such patients after euthyroidism has been achieved.

Polish Society of Endocrinology and Polish Diabetes Association recommendations on screening for thyroid dysfunction in type 1 and type 2 diabetes

Type 1 diabetes

1. TSH and thyroid peroxidase antibodies (TPOAb) should be measured in each patient with newly diagnosed type 1 diabetes, and in patients who have never undergone tests for thyroid hormonal function.
2. In patients with TPOAb titer above reference value and TSH concentration ≥ 2.0 mIU/L, fT4 concentration should be assessed and TSH concentration should be measured once a year.
3. Patients with TPOAb titer within reference values and TSH ≥ 2.0 mIU/L should undergo TSH tests every two years.
4. Patients with TPOAb titer within reference values and TSH < 2.0 mIU/L should undergo TSH tests every five years.
5. Patients with family history of hypothyroidism in a course of chronic autoimmune thyroiditis should be tested for TSH level once a year.
6. During every appointment with a diabetologist, patients should undergo clinical examination for thyroid dysfunction — in case of any abnormalities detected, TSH level ought to be assessed.
7. TSH level should be measured in diabetic patients with a poor lipid profile.
8. Measurements of TSH and TPOAb titer are advisable in the case of every female patient planning a pregnancy (particularly in the case of an unfavourable obstetric history).
9. Measurements of TSH and TPOAb titer are advisable in all female patients in the 4^{th}–8^{th} week of pregnancy (first obstetrician appointment).
10. TSH concentrations and anti-TSH receptor antibodies (TRAb) should be measured in all pregnant patients with a past medical history of Graves' disease between the 4^{th} and 8^{th} week of pregnancy (first obstetrician appointment). Moreover, a second TRAb titer assessment is recommended towards the end of the second trimester (before the 22^{nd} week of pregnancy).

Type 2 diabetes

1. TSH level should be measured in each patient with newly diagnosed type 2 diabetes, and in patients who have never undergone tests for thyroid hormonal function.
2. Patients with TSH ≥ 2.0 mIU/L should be tested for TPOAb.
3. In patients with TPOAb titer above reference value, diagnosis of type 2 diabetes should be reassessed e.g. anti-glutamic acid decarboxylase antibodies (anti-GAD Ab) should be measured.
4. In patients with TPOAb titer above reference value and TSH concentration ≥ 2.0 mIU/L, fT4 concentration should be assessed and TSH concentration should be measured once a year.
5. Patients with TPOAb titer within reference values and TSH ≥ 2.0 mIU/L should undergo TSH tests every two years.

6. Patients with TPOAb titer within reference values and TSH < 2.0 mIU/L should undergo TSH tests every five years.
7. During every appointment with a diabetologist, patients should undergo a clinical examination for thyroid dysfunction — when any abnormalities are detected, TSH level ought to be assessed.
8. TSH level should be measured in diabetic patients with a poor lipid profile.
9. Measurement of TSH level is advisable in the case of every female patient planning a pregnancy.
10. Measurements of TSH and TPOAb titer are advisable in all female patients in the 4th–8th week of pregnancy (first obstetrician appointment).
11. TSH concentrations and anti-TSH receptor antibodies (TRAb) should be measured in all pregnant patients with a past medical history of Graves' disease between the 4th and 8th week of pregnancy (first obstetrician appointment). Moreover, a second TRAb titer assessment is recommended towards the end of the second trimester (before the 22nd week of pregnancy).

Treatment

The aim of the treatment of thyroid dysfunction in diabetes mellitus is to achieve euthyroidism according to the adopted principles.

Treatment of primary hypothyroidism in diabetic patients

The first line treatment is a synthetic derivative of natural tetraiodothyronine — a medication containing levothyroxine sodium (LT4), in a daily dose individually determined for each patient. It has been demonstrated that subclinical hypothyroidism is an independent risk factor for cardiovascular episodes, which is of particular importance in the case of diabetic patients [17]. Therefore, treatment of subclinical hypothyroidism is recommended in this population.

Pregnancy and lactation [18]

It is necessary to treat both overt and subclinical hypothyroidism in pregnant patients. It should be noted that females with type 1diabetes — especially if an elevated TPOAb titer has been observed during pregnancy — are at a higher risk of developing postpartum thyroiditis. Consequently, females with type 1 diabetes should be tested for TSH levels six weeks, as well as three, six and nine months after delivery. L-thyroxine does not pass into breast milk, and hence there are no contraindications for breast-feeding mothers.

Treatment of primary hyperthyroidism in diabetic patients

The methods of treatment of hyperthyroidism both in the course of nodular goitre and Graves' disease in diabetic patients do not differ from the commonly accepted ones.

Nodular goitre

The treatment of choice for hyperthyroidism resulting from nodular goitre, irrespective of the concomitant diabetes, is almost always a radical one (thyroidectomy, radioiodine therapy).

Graves' disease

The first-line therapy — as in the case of non-diabetic patients — entails pharmacotherapy lasting 12–24 months (optimally 18 months). The aim of the treatment is to achieve a remission. Should this goal not be attained, the next step is radical therapy. The method of choice is radioiodine therapy; if this is contraindicated, thyroidectomy should be considered.

Thyroid orbitopathy

Infiltrative orbitopathy is most commonly treated with steroids. In diabetic patients, the optic nerve is more frequently affected. However, administering steroids in patients suffering both from diabetes and thyroid orbitopathy adversely influences the metabolic control of diabetes. Hence, in patients treated with oral anti-diabetic medications, this is a common indication for periodic insulin therapy. In certain cases, conducting a thyroidectomy prior to the treatment should be considered.

Pregnancy and lactation [18]

The principles of therapy remain the same as in the case of non-diabetic female patients.

The aim of hyperthyroidism treatment during pregnancy is to normalise the level of free thyroid hormones using as small doses of antithyroid medications as possible.

Thyroid disease and the treatment of diabetes

Subclinical forms of hypothyroidism, as well as hyperthyroidism, can lead to decompensation of diabetes, often in the form of hypoglycaemic episodes. A deterioration of metabolic control of diabetes and increased insulin requirement can be found in patients with diabetes and overt hyperthyroidism, particularly those treated with insulin. Since hyperthyroidism is most often accompanied by insulin resistance, administering metformin — if no contraindications arise — may

be worth considering. It should be noted that hyperthyroidism in diabetic patients can increase the risk of diabetic ketoacidosis [19].

Summary

Thyroid dysfunction is more common in diabetic patients than in the general population, and can adversely influence the metabolic control of diabetes. Therefore, patients suffering both from diabetes mellitus and thyroid disorders should be subject to separate diagnostic-therapeutic standards.

The presented paper

1. Determines the principles of carrying out screening tests for thyroid dysfunction in type 1 and 2 diabetic patients, including diabetic female patients planning a pregnancy and during pregnancy.
2. Stipulates the diagnostic and therapeutic guidelines for treating the abovementioned patients suffering from both subclinical and overt thyroid dysfunction, as well as for the necessary administration of steroids in thyroid orbitopathy.

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