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Thyroid – The Gland That Can Not be Neglected in Diabetes Patients

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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. Importantly, both hypothyroidism and hyperthyroidism can adversely affect metabolic control of diabetes. Thyroid diseases are most common autoimmune diseases in patients with diabetes, especially in type 1 diabetes. For the occurrence of these diseases are responsible genetic and environmental factors. Frequent coexistence of diabetes mellitus and thyroid diseases requires constant monitoring, measuring of thyroid hormones and anti-thyroid antibodies levels in patients with diabetes, according to recommendations of diabetic care. The goal of the treatment is to reach a stable euthyroid state. Particular attention should be paid for controlling thyroid function and diabetes during pregnancy.

Keywords: Diabetes; Autoimmune thyroiditis; Thyroid dysfunction; Thyroglobulin antibody (ATG); Thyroid peroxidase antibodies (TPO); Thyroid stimulating immunoglobulin (TSI); Thyroid stimulating hormone (TSH); Free thyroxine (fT4); Hypothyroidism; Hyperthyroidism.

1. Introduction

Diabetes mellitus and thyroid diseases represent two of the most common endocrinopathies, Thyroid disorders in both: type 1 and type 2 diabetes are frequent [1-3]. Recently, Polish authors presented problem of thyroid disorder in patients with metabolic syndrome [4].

Disorders of thyroid functions may influence the level of diabetes metabolic balance, therefore early diagnosis and correct treatment are fundamental.

Comprehensive overview of diagnosis and treatment rules of these disorders was presented in publication elaborates common statement of Polish Diabetes Association and Polish Society of Endocrinology [5].

It is worth to notice that the present diabetes classification becomes less valid in conjunction with current knowledge.

Genetic and immune examinations have spread knowledge about ethiopathogenesis of glucose metabolic disorders and indicates to revise existing diabetes classification. The decision should be taken in next years. There are more and more evidences that the current classification has to be verified in view of present state of knowledge.

Among others, the division between type 1 and type 2 diabetes is questioned [6].

The opinion that both types of diabetes are one disease caused by insulin shortage and insulin resistance. The difference of these two types is an effect of progress dynamic of each of these disorders. In 2001, the „accelerator hypothesis" that matches development of insulin sensitivity disorders with different genetic determinants [7, 8].

The progress in diagnostics based on immune and genetic examinations highlights need of setting new diagnosis standards. It is acknowledged that 10% of diabetes cases can not be classified acc. to current divisions [9].

Right now, the present classification, with some simplifications, is in use.

However the mechanisms of autoimmunization have not been elucidated definitively, it is known that genetic and environmental factors are responsible for tolerability loss of immune system.

2. Autoimmune Disorders Diabetes Associated

The autoimmune thyroid disorders, celiac illness and gastritis are the most frequently observed diabetes-associated concomitant diseases of autoaggression [10-14].

The autoimmune processes that lead to pancreatic islets destruction may also affect other organs [15, 16].

It is important to know that sometimes these disorders can occur ahead of diabetes. Early diagnosis of autoimmune processes improves selection of group of high-risk patients who requires specially careful observation. At this stage, these patients may already be in subclinic alphase of illness [17].

Early diagnosis and proper treatment improves metabolic control of diabetes, reduce risk of complications and has profitable influence on the quality of patient life [18-20].

Due to fact that type 1 diabetes has an autoimmune pathogenesis, it can be the part of polyendocrinopathy.

Type 1 diabetes may be a part of polyendocrinopathy because it has an autoimmune pathogenesis. The common genetic background is underlined also by fact that in patients with illnesses of autoaggression haplotypes containing antigens: HLA-DR3, HLA-DR4 or HLA-DR5 are identified most frequently [21].

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The genetic backgrounds of autoimmune thyroiditis and diabetes were analyzed also by other authors [22].

This is indicated, among others, by the results of a study recently conducted by Polish authors who indicated the frequency of linking the occurrence of autoimmune thyroiditis with DQA1 and DRB1 alleles HLA genotype [23].

Other authors have also made similar observations [24].

Both these diseases are classed as autoimmune polyendocrine syndromes [25-44].

Recently, such observations were conducted in a group of 25,759 patients with type 1 diabetes presented by the American authors [32].

At the beginning the process progress is asymptomatic or barely symptomatic.

It was observed that during the course of different autoimmune illnesses similar autoimmune phenomena occurred, such as: organ-specific antigen formation, presence of lymphocytic infiltrations in specific organs and immune system disorders.

In type 1 diabetes patients, besides antibodies characteristic for diabetes such as islet cell antibodies (ICA), antibodies against glutamic acid decarboxylase (anty-GAD), against protein tyrosine phosphatase (ant-IA2) and against insuline (IAA), antibodies against antigens of various organs occur.

Discussed this issue recently Hwang, *et al.* [34].

As was mentioned above, the most frequent diabetes-associated concomitant diseases are thyroid disorders. It is common for patients in all age groups.

However, as far as early diagnosis conditions of these disorders for type 1 diabetes juvenile patients are quite precisely described, in LADA diabetes young adult patients these illnesses remain often undiagnosed for long time [29, 44].

Until now, autoimmune thyroid dysfunctions have been mainly associated with type 1 diabetes. Currently, more and more often the attention to the presence of autoantibodies also in type 2 diabetes should be counted with the possibility of thyroid dysfunction in patients with type 2 diabetes [27, 42]. This requires further research.

Thyroid functions changes and its hormones concentration in the course of diabetes consist in:

- impairment of peripheral deiodination of T4 (low T3 syndrome)
- disfunction of HPT axis - hypothalamus-pituitary-thyroid
- concomitance of diabetes and autoimmune thyroid diseases.

Low T3 syndrome is characterized by rapid decrease of concentration of circulating T3 and concomitant increase of rT3. The drop of oxygen glycolysis intensity in adipose tissue and slow lipolysis decrease glucose requirements. In effect, intensification of hyperglycemia and insulinemia increase are observed.

Apart from thyroid hormones peripheral metabolism disorders, another anomaly is dysfunction of HPT axis - hypothalamus-pituitary-thyroid that leads to impaired thyrotropin (TSH) secretion and causes changes in T3 and T4 concentrations.

In most cases, clinical course of diabetes-associated concomitant autoimmune diseases is „clinically silent" what makes their diagnosis difficult. Therefore, determination of these disorders markers and screening immediately after diabetes diagnosis is essential.

The markers for evaluation of thyroid functions are levels of T3, T4 and TSH thyroid hormones in serum and also levels of thyroid antigens antibodies: against thyroid peroxidase (a/TPO), against thyroblobulin (a/TG) and againts TSH receptors (TRAb).

3. Diabetes-Associated Concomitant Autoimmune Thyroid Disorders

They have very composite clinical picture: from hypothyroidism with inflammation (Hashimoto disease) via subclinical changes without or with very discrete thyroid disorders to fully symptomatic hyperthyroidism (Graves-Basedow disease).

The presence of thyroid antibodies is not equal to diagnosis of this organ dysfunction [26].

Concomitant autoimmune thyroid disorders deteriorate course of diabetes [31].

Recently, Polish authors presented multi-center researches on type 1 diabetes juvenile patients which show that autoimmune thyroiditis is associated with worsening metabolic control of diabetes [37].

This information confirms previous statements of these authors about necessity of early diagnosis and treatment of autoimmune thyroiditis in diabetes patients [25, 45].

Thyroid hormones have diabetogenic effect. Moreover hyperthyroidism inducts insulin resistance of tissue. Unstable course of diabetes and hyperthyroidism concomitant intensified metabolism increase risk of ketoacidosis occurrence. On another hand, thyroid hormones insufficiency inhibits gastro-intestinal absorption of glucose, glicogenolysis and gluconeogensis as well as increases insulin sensitivity. Therefore in diabetes patients concomitant hypothyroidism may increase risk of hypoglycemia, especially under fasting conditions and contributes to lipid storage diseases.

Special attention should be paid to monitoring thyroid functions in diabetes female patients who plan pregnancy as well as these who are pregnant [46].

Comprehensive overview of thyroid dysfunctions during pregnancy was presented by Polish authors [47].

Also other authors consider this question [48, 49].

It is important to know that thyroid disorders become especially relevant when they accompany diabetes. In this case, there are two diseases that threaten correct fetal development. These patients require special control and therapy. The guidelines for this kind of treatment during pregnancy as well as confinement were developed [5].

In order to ensure early diagnosis of thyroid diseases in diabetes patients it is recommended to identify level of antibodies and perform ultrasonographic examination of thyroid just after diabetes is diagnosed. In patients with increased antibodies level and/or changes in USG result, the thyroid hormone should be estimated [50].

The value of USG examination in patients without evident clinical symptoms of thyroid disease was described by Junik et all [51].

Based on literature overview, English authors presented risks of thyroid disorders in diabetes patients [52].

Authors discussed thyroid dysfunction influence on glucose metabolic disorder as well as on cardiovascular system diseases.

Similar observations were recently presented by Italian authors, who confirmed correlation between vascular complications with increase of antibodies against thyroid hormones (THAb) level and long-lasting type 1 diabetes in young adult patients [53].

Indications to evaluation of thyroid antibodies level in long-lasting type 1 diabetes patients were described also in recently published researches of Polish authors [54].

Chronic lymphocytic thyroiditis, known as Hashimoto disease, is the most frequent cause of hypothyroidism acquired in developmental age as well as in adults.

Hashimoto disease may develop in ca. 25% of adult type 1 patients and presence of thyroid antibodies. The currently known thyroid antigens contributing in autodestructive process are: thyroperoxidase (TPO), thyroglobuline (ATG) and TSH receptors. The thyroid tissue destruction is an effect of gland infiltrating by lymphocytes and subsequent thyrocytes destruction by cytotoxic T lymphocytes or is a consequence of hormonal reaction of antibodies against thyroid antigens. There are more and more cases when the intensified apoptosis was a pathogenetic factor.

The clinical picture of autoimmune thyroiditis is not typical and diversified. In majority of patients with autoimmune thyroiditis and hypothyroidism there are no clinical symptoms of the disease. The diagnosis is based on low concentration of total thyroxine (T4), free thyroxine (fT4) and increased concentricity of TSH in serum, high level of TPO antibodies and/or ATG and specific picture in USG result.

The clinical symptoms of hypothyroidism occur late and are preceded by destruction of major part of the gland.

In the early phase of Hashimoto type thyroiditis, the ATG antibodies level is high and TPO antibodies level is only slightly increased, than ATG may disappear while TPO are present for many years. Antibodies against TSH receptors block thyrocytes ability to synthesis of thyroid hormones and are detected only in patients with thyroiditis and hypothyroidism.

The concentration of these antibodies correlates with the stage of hypothyroidism.

Multiglandular hormone deficiency has complex clinical implications.

Inhibited gastro-intestinal absorption of glucose and decrease of glycogenolysis and gluconeogenesis are observed in hypothyroidism.

The impaired glucose tolerability may be associated with decreased insuline secretion, correlated probably with increased insulin sensitivity.

The screening tests performed immediatly after diabetes diagnosis and their systematic replication during its course enable to diagnose thyroid dysfunctions at early phase what can prevent from progress of explicit hypothyroidism with all of its consequences.

The primary goal of hypothyroidism treatment is an early replacement therapy what ensures correct diabetes metabolic balance and, in effect, decreases number of late complications of diabetes.

Autoimmune thyroiditis with hyperthyroidism is a metabolic disorders syndrome that results from chronic excess of thyroid hormones in the system. This disease occures mainly as a Graves-Basedow disorder and has autoimmune background: circulationg in the patients blood antibodies against TSH receptors - antireceptors antibodies (TSI - thyroid stimulating immunoglobulin), which correlate with disease process intensification, stimulate thyroid to exaggerated synthesis of thyroxine and thiiodothyronine hormones.

In blood of Graves-Basedow patients, there are other antibodies which indetify antygenic structures of thyroid epithelial cells.

These changes are probably caused by weakened activity of suppressor lymphocytes which are able (in physiological conditions) to identify and destroy autoreactive T-cell clones which target ntigenic structures of thyroid epithelial cells.

In healthy people, the thyroid hormones secretion is regulated by feedback on hypothalamin-pituitary axis trough TSH.

When the thyroid is stimulated by immunoglobulins circulating in the blood but without control of hypothalamin-pituitary axis, the thyroid hormones level increased without regard to body needs.

The incidense of Graves-Basedow disease in type 1 diabetes patients is estimated between 1 to 2% and is higher than in general population.

Clinical symptoms of this disease are quite characteristic. The diagnosis depends on hormonal examination (concentration of T3, T4 or their free fractions and TSH in serum), identification of antibodies TSI (thyroid stimulating immunoglobulin) and heterogenous echogenicity of thyroid gland in USG examination.

The presence of antireceptor antibodies TSI is identified in 90% of patients. Their presence and level correlate with disease process intensification.

In contrast to Hashimoto disease or diabetes, clinical manifestation of Graves-Basedow illness occurs early - it is minimally predated only by gland destruction.

The course of diabetes in patients with concomitant hyperthyroidism is usually very unstable: blood glucose levels difficult to balance, increased insulin requirements mainly as an effect of progressing insulin resistance.

4. Subclinical Forms of Thyroid Dysfunctions

Most frequently it is a subclinical hidden hypothyroidism without clear clinical symptoms of hypothyreosis, with correct T4 or fT4 concentration and slightly increased TSH level before or after thyroliberin (TRH) administration.

The subclinical form of hyperthyroidism is characterized by lack of clear clinical symptoms of hyperthyreosis, correct thyroid hormones concentrations and decreased TSH level.

The indications to treatment of subclinical forms of thyroid dysfunctions are questionable.

Information about benefits from L-thyroxine low doses treatment initiated in patients with subclinical hypothyroidism indicates that this kind of therapy is entirely justified.

5. Description of Cases

Case 1. In 9 year old girl type 1 diabetes was diagnosed. Examination showed: increased level of anti-pancreatic autoantibodies and anti-thyroid antibodies ((a/TPO – 157 IU/ml, ATG – 102 IU/ml), STH level in the upper limit (3,94 mIU/l). In USG examination, heterogenous gland structure and numerous hypoechogennic forms corresponding to thyroid nodules were indentified which re in favour of lymphocytic thyroiditis. Hormonal therapy was initiated . In next years hormonal replacement therapy was continued and increased concetrations of antibodies persist during euthyreosis.

During this period, the diabetes metabolic balance was very good (HbA1c 6%). During 3 years observation, the development of the child and the gestation period were correct. Intensive insulin therapy and L-thoryxine replacement were maintained.

Case 2. In 12 year old boy type 1 diabetes was diagnosed. Apart from increased anti-pancreatic autoantibodies (a/GAD) level, high a/TPO titre (901 IU/ml), decreased STH concentration (0,045 mIU/ml) and increased fT4 level (4,5mg/ml) were observed. USG examination showed gland heterogenously echogennic in its entirety with numerous hypoechogennic regions. Thyrotoxicosis was diagnosed and the pharmacotherapy was initiated.

The treatment of hyperthyroidism was continued for 2 years. The stage of diabetes balance was unstable during this period. Correct metabolic control was difficult to achieve and maintain. After 3 years of treatement, the stable euthyreosis was achieved and antithyroid medications were discontinued.

The diabetes metabolic balanse was improved. After 10 months, clinical and laboratory symptoms of hyperthyroidism recurred and radioiodine therapy was started.

Case 3. 37 year old patient with type 2 diabetes diagnosed 4 years before, was treated with insuline mixtures without selfcontrol. During diabetes consultation chronic unbalance of diabetes was diagnosed - HbA1c 8,4%. Due to young age and slim silhouette of patient, diagnosis of LADA type diabetes was taken into account in differential considerations.

Performed examinations proved suspicions: low level of C-peptide (< 0,1 ng/ml), very high titre of a/GAD autoantibodies (1251 IU/ml), increased TSH level (4,21 mlU/l) and increased a/TPO titre (161,6 IU/ml). Based on examination results, autoimmune thyroiditis with hypothyroidism was diagnosed.

Intensive selfcontrol, intensive insulin therapy based on insulin analogs and hormonal treatment of hypothyroidism were recommended.

Examinations performed year after the first visit revealed improvement of diabetes metabolic balance and euthyreosis state. Further increase of autoantibodies a/GAD (> 2000 IU/ml) and a/TPO (339,1 IU/ml) titres were indetified.

Case 4. 45 year old patient with diabetes diagnosed 2 years before was initially treated with small doses of insulin but due to lifestyle change (diet and increase of physical activity) the insulin requirements decreased, insulin therapy was finished and metformin treatment was initiated. During diabetes consultation, incorrect trend of the curve after oral glucose tolerance test, HbA1c 6,21%, C-peptide 1,08 ng/ml and very high a/GAD autoantibodies titre: > 2000 IE/ml were revealed. The type LADA diabetes was diagnosed and small dose of insulin analog was initiated. In effect improvement of glycemic balance. An extended diagnostics showed increased a/TPO autoantibodies titre (146,2 IU/ml) with correct thyroid hormones level. Next examination revealed decrease of C-peptide level (0,69 ng/ml) and maintained high titre of a/GAD autoantibodies, increase of ICA and IA2 autoantibodies titres as well as a/TPO autoantibodies titre (240,7 IU/ml). The thyroid hormones level was within normal range continually.

6. Discussion

In presented cases, two improprieties in both adult patients should be considered (case no 3 and 4). The first one concerns differentiating of diabetes types and consequent incorrect treatment. The second perteins lack of screening tests for thyroid dysfunctions. As far as in juvenile patients, this kind of test was performed according current reccommendation of Polish Diabetes Association [55], in adult patients screening was not executed.

7. Conclusions

Latent Autoimmune Diabetes in Adults (LADA) is a form of autoimmune-mediated diabetes in adults [56, 57].

Patients with LADA have a higher prevalence of thyroid autoimmune markers. Screening for autoimmune thyroid diseases in patients with LADA should be done similarly to type 1

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