Netherlands
The Journal of Medicine

REVIEW

Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review

A. Van den Driessche, V. Eenkhoorn, L. Van Gaal, C. De Block*

Department of Diabetology and Endocrinology, Antwerp University Hospital, Edegem, Belgium,
*corresponding author: tel.: 32-3-821 32 78, fax: 32-3-825 49 80, e-mail: christophe.de.block@uza.be

ABSTRACT

Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of insulin-producing β cells and is characterised by the presence of insulitis and β-cell autoantibodies. Up to one third of patients develop an autoimmune polyglandular syndrome. Fifteen to 30% of T1DM subjects have autoimmune thyroid disease (Hashimoto's or Graves' disease), 5 to 10% are diagnosed with autoimmune gastritis and/or pernicious anaemia (AIG/PA), 4 to 9% present with coeliac disease (CD), 0.5% have Addison's disease (AD), and 2 to 10% show vitiligo. These diseases are characterised by the presence of autoantibodies against thyroid peroxidase (for Hashimoto's thyroiditis), TSH receptor (for Graves' disease), parietal cell or intrinsic factor (for AIG/PA), tissue transglutaminase (for CD), and 21-hydroxylase (for AD). Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease.

Hashimoto's hypothyroidism may cause weight gain, hyperlipidaemia, goitre, and may affect diabetes control, menses, and pregnancy outcome. In contrast, Graves' hyperthyroidism may induce weight loss, atrial fibrillation, heat intolerance, and ophthalmopathy. Autoimmune gastritis may manifest via iron deficiency or vitamin B12 deficiency anaemia with fatigue and painful neuropathy. Clinical features of coeliac disease include abdominal discomfort, growth abnormalities, infertility, low bone mineralisation, and iron deficiency anaemia. Adrenal insufficiency may cause vomiting, anorexia, hypoglycaemia, malaise, fatigue, muscular weakness, hyperkalaemia, hypotension, and generalised hyperpigmentation.

Here we will review prevalence, pathogenetic factors, clinical features, and suggestions for screening, follow-up and treatment of patients with T1DM and/or autoimmune polyglandular syndrome.

KEYWORDS

Autoantibodies, autoimmune polyglandular syndrome, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM), arising through a complex interaction of immune, genetic and environmental factors, results from autoimmune destruction of insulin-producing β cells. T1DM is characterised by the appearance of insulitis and the presence of β-cell autoantibodies.[1] In up to one third of patients the autoimmune attack is not limited to β cells, but expands into an autoimmune polyglandular syndrome.[2-8] Of type 1 diabetic subjects, 15 to 30% have autoimmune thyroid disease (Hashimoto's or Graves' disease), 5 to 10% are diagnosed with autoimmune gastritis and/or pernicious anaemia (AIG/PA), 4 to 9% present with coeliac disease (CD), 0.5% have Addison's disease (AD), and 2 to 10% show vitiligo (*table 1*).[2-8]

In this clinical review we will discuss prevalence, predisposing factors (age, immune, genetic, environmental), clinical presentation, and suggestions for screening, follow-up and treatment of patients with type 1 diabetes and/or autoimmune polyglandular syndrome.

AUTOIMMUNITY

Organ-specific autoimmunity is frequent in T1DM subjects. This might be due to the fact that these patients show multiple immunological abnormalities. These include an imbalance in B and T lymphocytes, or an increased tendency to react strongly against certain antigens or a (genetically determined) poor ability to develop tolerance to autoantigens.[1,6] Individuals with one autoimmune disease are known to be at increased risk for other autoimmune processes.[3]

Table 1. *Prevalence of organ-specified autoantibodies and autoimmune diseases*

Disease or AB	General population	Type 1 diabetes mellitus	Coeliac disease	Addison's	Hypothyroidism
Type 1 diabetes mellitus anti-islet AB	2-3% 1-3%	xxx 85-90%		12-14%	4%
Coeliac transglutaminase AB	0.5% 0.5-1%	1-8% 8-12%	xxx 99%	5%	4%
Addison's 21-hydroxylase AB	0.005% 0-0.6%	0.5% 0.7-3%		xxx 83-90%	
Hypothyroidism	5-9%	30%	3-12%	14-21%	xxx
aTPO	2-10% in adults 1-4% in children	15-30% in adults 5-22% in children	18%	23-40%	47-83%
Graves' TSH receptor AB	0.1-2% ?	6-10% ?		10-20%	
Pernicious anaemia/ autoimmune gastritis	2% for AIG 0.15-1% for PCA	5-10% for AIG 2-4% for PCA		6%	2%
PCA	2.5 - 12%	15-25% in adults 10-15% in children			

AB = antibody; AIG = autoimmune gastritis; PCA = parietal cell antibodies; T1DM = type 1 diabetes mellitus.

Most of the autoimmune endocrine disorders appear initially as infiltration of the gland by lymphocytes and macrophages. This may lead to destruction and atrophy of the gland with deficiency of its hormone. The destructive process is presumed to be T-cell mediated. Antibodies to certain antigens of the gland, mostly intracellular enzymes, appear in the blood. These include thyroid peroxidase (for Hashimoto's thyroiditis), thyroid stimulating hormone (TSH) receptor (for Graves' disease), parietal cell or intrinsic factor (for autoimmune gastritis/pernicious anaemia), endomysial or tissue transglutaminase (for CD), and 21-hydroxylase antibodies (for AD).[2-8] The role of such antibodies remains unclear, but they are important as diagnostic messengers and appear commonly before clinical hormone deficiency. Thus screening for these antibodies allows early detection and the potential to prevent significant morbidity related to unrecognised disease. However, the frequency of screening for and follow-up of patients with positive autoantibodies remain controversial.

There are several direct links between genetics and autoimmune disease: the developmental maturation of T cells in a genetically susceptible individual occurs through molecular interactions between the T-cell receptor and the HLA-antigen complex. Selection of T cells with receptors likely to contribute to autoreactivity may preferentially occur in the context of specific HLA-DQ alleles that are prone to diabetes, autoimmune thyroid disease, AD, CD, and other auto-immune diseases.[3,9-12] Indeed, disease-prone HLA molecules may be ineffective at binding and presenting peptides derived from tissue-specific antigens, and such a poor presentation in the thymus could impair mechanisms of negative selection allowing autoreactive T cells to survive the passage through the thymus. Subsequent activation of these T cells in the context of recognising islet-associated antigens can trigger a poorly regulated immune response that results in progressive tissue destruction.

Other important genetic factors include the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), the MHC I-related gene A (MIC-A) and the protein tyrosine phosphatase nonreceptor type 22 (PTPN22).[11-14] The CTLA-4, being expressed on activated CD4+ and CD8+ T-cell membranes, inhibits T-cell activation by binding costimulatory molecules. Polymorphisms within the CTLA-4 gene have been associated with T1DM and autoimmune thyroid disease, particularly the CT60 A/A polymorphism, and with Addison's disease.[13,14] The MIC-A protein is expressed in the thymus and is thought to interact with a receptor, NKG2D, which may be important for thymic maturation of T cells.[15] NKG2D regulates the priming of human naive CD8+ T cells, providing a possible explanation for the association with autoimmune diseases.[16] MIC-A polymorphisms have also been linked to T1DM, (the 5 allele and 5.1 allele),[17] coeliac disease (allele 4 and 5.1),[18,19] and Addison's disease (allele 5.1).[20] The PTPN22 gene is expressed in T cells, encoding for lymphoid tyrosine phosphatase (LYP). A specific polymorphism at position 620 (Arg → Trp) may decrease that ability of LYP to interact with its target molecules and down-regulate T-cell receptor signalling.[21,22] This has been observed in Graves' disease and weakly in Addison's disease.[23]

AUTOIMMUNE POLYGLANDULAR SYNDROMES

In 1866, Ogle was the first to describe the association between diabetes mellitus and Addison's disease. However, the adrenal insufficiency in this case was due to tuberculosis. In 1910, Parkinson first described a patient with coexisting diabetes and pernicious anaemia. In 1926, Schmidt reported two cases of Addison's disease associated with lymphocytic thyroiditis.[24] In 1931, Rowntree and Snell

described the unprecedented findings of an association between Addison's disease, Graves' disease and T1DM. A year later Gowen reported the first case of Addison's disease, Hashimoto's thyroiditis and T1DM.

The presentation of these autoimmune diseases as associated disorders led to the definition and classification of autoimmune polyendocrine syndromes I and II, by Neufeld, Maclaren and Blizzard in 1980.[25] Both are associated with type 1 diabetes in about 20% of cases.[3] The autoimmune polyendocrine syndrome I (APS-I), also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED), is a rare polyendocrine autoimmune disease caused by mutations of the autoimmune regulator gene (AIRE).[3,26] It is inherited in an autosomal recessive manner. APS-I is defined by the presence of two or three of the following components: mucocutaneous candidiasis, adrenal insufficiency and/or hypoparathyroidism. It usually manifests in infancy at age 3 to 5 years or in early adolescence. The female-to-male ratio varies between 0.8/1 and 2.4/1. The autoimmune polyendocrine syndrome II (APS-II) is defined as the association of an autoimmune endocrine disorder with an additional autoimmune disease but not meeting criteria for APS-I and not having an identified mutation of the AIRE gene. APS-II is a complex polygenic disorder. By definition, patients with T1DM and an additional autoimmune disease meet the criteria for APS-II. In the majority of T1DM patients, the associated autoimmune disease follows the onset of diabetes. The prevalence of APS-II is 1/20,000 with a female preponderance (male/female ratio = 1/3). This syndrome has a peak incidence between the ages of 20 and 60 years, mostly in the third or fourth decade.

TYPE 1 DIABETES

T1DM is a T-cell mediated autoimmune disease that develops in genetically susceptible individuals and results in destruction of insulin-producing β cells.[1,27] Several lines of evidence support the autoimmune nature of the β-cell destructive process:

- Infiltration of the pancreatic islets by lymphocytes and macrophages (insulitis);[28]
- Presence of autoantibodies to islet cell antigens (ICA), tyrosine phosphatase IA-2 (IA2A), glutamic acid decarboxylase-65 (GADA), insulin (IAA), and zinc transporter ZnT8 (Slc30A8);[1,27,29]
- A preferential occurrence of T1DM in persons carrying specific allelic combinations at immune response loci within the HLA gene complex;[9]
- Increased prevalence of organ-specific autoimmune disorders in T1DM;[2-8]
- The disease can be transferred by spleen or bone marrow cells;[30]
- Animal models of T1DM (NOD mouse, BB rat) that show a defect in immunoregulation contributing to the onset of disease.

One or more β-cell autoantibodies are present in approximately 90% of new-onset patients with type 1 diabetes.[27] They appear to develop sequentially. Insulin autoantibodies are often the first expressed, especially in younger children.[31-33] GADA positivity is suggested to represent a propensity for general autoimmunity, while IA2A positivity may be a more specific marker of β-cell destruction.[4,34] Beta-cell autoantibodies also represent important preclinical markers of the disease as they may be present for years before the diagnosis of diabetes.[33,35] The risk of diabetes for a first-degree relative depends on the number and type of antibodies that are present. Family members who express IAA, GADA and IA2A have a 75% risk of developing T1DM within the next five years, as compared with a 10 to 25% five-year risk in those expressing only one of the antibodies. Data from the Belgian Diabetes Registry show a five-year risk for T1DM of 34% in subjects positive for ≥3 antibodies. Progression to diabetes amounted to 12% within five years among siblings positive for IAA, 20% for ICA, 19% for GADA but 59% for IA-2A. IA-2A were detected in 1.7% of all siblings and in 56% of the prediabetic subjects on first sampling.[36]

Among genes associated with T1DM, the HLA gene complex on chromosome 6p21 (IDDM1) is the genetic factor with the strongest association.[37] The IDDM2 gene located on chromosome 11p15 in the upstream region of the insulin gene also confers susceptibility to T1DM.[38,39] IDDM1 and IDDM2 are estimated to contribute to about 40 to 50% and 10%, respectively, of familial clustering of type 1 diabetes.[40] Multiple additional genes also contribute to diabetes susceptibility. One of these is IDDM12 on chromosome 2q33, which contains two autoimmune disease candidate genes: CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and CD28, encoding for T-cell receptors involved in controlling T-cell proliferation.[41] Other important genes include the MHC I-related gene A (MIC-A) and the protein tyrosine phosphatase nonreceptor type 22 (PTPN22),[11] as discussed above.

Ninety percent of Caucasian T1DM patients express the HLA DR3 and/or DR4 alleles. These HLA alleles are expressed in 40% of the general white population.[37,42] Expression of HLA DR2 is decreased in persons with diabetes. Certain combinations of HLA alleles are found with a frequency greater than expected and are thus not randomly distributed within the general population. This phenomenon is called linkage disequilibrium. Particularly, HLA DQA1*0301-DQB1*0302 (in linkage disequilibrium with DR4) and DQA1*0501-B1*0201 (in linkage disequilibrium with DR3) haplotypes confer a high

diabetogenic risk.[43-45] The absolute risk of a child with this DR3/DR4 genotype developing T1DM from the general population is similar to a first-degree relative of a T1DM patient (1 in 20). DQB1*0602 and DQA1*0102 alleles are associated with dominant protection.

The Eisenbarth model of T1DM as a chronic autoimmune disorder begins with environmental triggers in genetically susceptible persons, progressing to autoimmunity with appearance of β-cell antibodies, further evolving towards metabolic dysregulation with loss of first-phase insulin response (FPIR), increasing HbA1c within the normal range, impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT), and finally resulting in overt diabetes and loss of C-peptide.[11]

The first-phase insulin response (FPIR) measured by iv glucose tolerance testing is the sum of insulin levels the first and third minute after administration of an iv glucose load. Many subjects with T1DM had a low FPIR before the diagnosis of diabetes, and this may persist for years before clinical disease onset.[46,47] These data suggest that subjects go through a phase of decreasing β-cell mass. The exact β-cell mass at diagnosis is poorly defined. For patients with long-term type 1 diabetes, it is usually decreased to less than 1% of normal.[48] Data from the Belgian Diabetes Registry demonstrate that residual β-cell function can also be analysed according to the measurement of C-peptide release as induced by a hyperglycaemic clamp procedure.[49] Low first phase C-peptide response specifically predicts impending diabetes while a low second phase response probably reflects an earlier disease stage. Clamp-derived parameters may improve selection and monitoring of first-degree relatives in future prevention trials.[50]

A typical *de novo* type 1 diabetes patient presents with hyperglycaemia and polyuria, polydipsia and weight loss. Ketoacidosis is common. We suggest to verify autoantibody status at the moment of diagnosis of type 1 diabetes.

The association between T1DM and organ-specific autoimmune disease can be explained by sharing a common genetic background (HLA antigens), but also by a defective immunoregulation.

AUTOIMMUNE THYROID DISEASE

Autoimmune thyroid diseases (AITD) include Hashimoto's thyroiditis and Graves' disease. Hashimoto's thyroiditis, first described in 1912,[51] is the most prevalent autoimmune disease associated with T1DM.[51] Hashimoto's thyroiditis is defined by the presence of thyroid peroxidase (TPO) or thyroglobulin antibodies, and elevated TSH concentrations in the absence of medications.[52] Although many subjects with Hashimoto's thyroiditis are hypothyroid, there is a subgroup of thyroid autoantibody-positive cases who are euthyroid. It may take years for those subjects to develop thyroid disease. The 20-year follow-up study of the Whickham cohort demonstrates that TPO antibodies are predictive of thyroid failure with an annual incidence of 4.3% in subjects with an initial elevated TSH level (>5.0 μU/ml). TSH is also predictive of thyroid failure. At a TSH level of 5 μU/ml the probability of hypothyroidism is 0.5% per year. Higher initial serum TSH or thyroid antibody concentrations predicted higher rates of progression.[53]

Thyroid peroxidase antibodies (aTPO) are present in 15 to 30% of adults and in 5 to 22% of children with type 1 diabetes, compared with 2 to 10% and 1 to 4%, respectively, in matched controls (*table 1*).[4,6-8,54-56] The prevalence of subclinical hypothyroidism in type 1 diabetic patients is estimated at 13 to 20%,[4,7,8,54] compared with 3 to 6% in a nondiabetic population, with a preponderance for older female patients.[53] Up to 50% of TPO-antibody-positive T1DM patients progress to overt autoimmune thyroid disease. Conversely, 2.3% of children with AITD have islet cell antibodies compared with 0% of controls. Cross-sectional analysis has shown that hypothyroidism is present in 4 to 18% of subjects with T1DM.[4,56-58] Long-term follow-up suggests that as many as 30% of patients with T1DM will develop AITD.[59] T1DM subjects with GADA positivity, in contrast to IA2A-positive patients, are more prone to have aTPO.[4,60] The association of GADA with thyrogastric antibodies might be explained by the fact that GAD-65 is not exclusively present in the brain and pancreas but can also be found in the thyroid gland and stomach.[60] T1DM patients with persisting ICA positivity for more than three years or with GADA+ are at increased risk of thyrogastric autoimmunity.[8,61,62] Other factors such as age, diabetes duration, and gender (female preponderance) influence the link between T1DM and AITD.

At-risk haplotypes for Hashimoto's thyroiditis are the HLA DQA1*0301 (linked to DR4), DQB1*0301 (linked to DR5) and DQB1*0201 (linked to DR3).[10,65] The HLA haplotype DR3-DQB1*0201 contributes to the genetic susceptibility to T1DM, AITD and autoimmune polyglandular syndrome II. Other loci (VNTR and CTLA-4) may also contribute to the clustering and may influence disease phenotype and severity, as discussed above.

A symmetric, painless goitre is usually the first presentation in Hashimoto's thyroiditis, although about 10% of patients have atrophic thyroid glands. Treatment of hypothyroidism is important because the decrease in basal metabolism may cause weight gain, hyperlipidaemia, atherosclerotic heart disease, goitre, and may affect diabetes control, growth, menses, and increase the risk of adverse pregnancy outcome. Even more, the presence of autoantibodies may be associated with an increased likelihood of spontaneous abortion, even in the absence of overt disease. Although thyroid lymphoma is very rare, the risk of this disease is increased 67-fold in patients with Hashimoto's thyroiditis.

Treatment of Hashimoto's hypothyroidism consists of suppletion of levothyroxine sodium. The goal of replacement therapy is to normalise serum TSH levels.[52]
Current recommendations from the American Diabetes Association are to screen T1DM patients for dysthyroidism using TSH after stabilisation at onset of diabetes, or in case of symptoms of hypothyroidism or hyperthyroidism, and every one to two years thereafter.[66] Since patients who are TPO-antibody positive have an 18-fold increased risk of developing thyroid disease compared with patients who are TPO-antibody negative, we and others suggests to screen T1DM patients using TPO autoantibodies, TSH and T4 levels at onset of T1DM and yearly thereafter.[2]

Autoimmune hyperthyroidism is less common. Robert Graves first identified the association of goitre, palpitations, and exophthalmos in 1835, although Caleb Parry had published details of a case ten years earlier.[65] Graves' hyperthyroidism is caused by thyroid stimulating antibodies that bind to and activate the TSH receptor on thyroid cells (TSH-receptor antibodies).[66] These antibodies not only cause hypersecretion of thyroid hormone, but also promote hypertrophy and hyperplasia of thyroid follicles, resulting in a goitre. Graves' disease shares many immunological features with Hashimoto's thyroiditis, including high serum concentrations of antibodies against thyroglobulin and thyroid peroxidase. Thyroid function tests reveal a suppressed TSH level, elevated levels of serum T4 and T3, and positive TSH receptor antibodies.[66]
Graves' disease affects approximately 0.5% of the general population and is the underlying cause of 50 to 80% of cases of hyperthyroidism.[66] Subclinical hyperthyroidism can be diagnosed in 6 to 10% of T1DM patients, compared with 0.1 to 2% in the nondiabetic population (*table 1*).[4,58,59]
The incidence of overt hyperthyroidism in persons with a suppressed serum TSH is calculated at 2 to 4% per year. Women are five to ten times more at risk of developing Graves' disease than men. Stress may trigger the disease. At-risk haplotypes for Graves' disease are DQA1*0501 (linked to DR3 and to DR5), and DQB1*0302 (linked to DR4).[67,68]
The severity and duration of Graves' disease and the age of the patient determine the manifestations of hyperthyroidism: nervousness, emotional lability, disturbed sleep, fatigue, palpitations and atrial fibrillation, heat intolerance, weight loss, and Graves' ophthalmopathy.[66] Among patients treated with insulin for diabetes, hyperthyroidism increases insulin requirements. Hyperthyroidism may aggravate glucose intolerance by multiple mechanisms, which include increased hexose intestinal absorption, increased glucose production (gluconeogenesis and glycogenolysis), and decreased responsiveness to insulin.
Current treatment of Graves' hyperthyroidism consists of antithyroid drugs (propylthiouracil or methimazole), radioactive iodine, and surgery. Antithyroid drugs are effective in controlling hyperthyroidism because they inhibit thyroid hormone production and may have an immunosuppressive effect, causing a decrease in the levels of TSH receptor antibodies. No consensus exists regarding the treatment of subclinical hyperthyroidism despite arguments suggesting that therapy with antithyroid drugs may be indicated to prevent atrial fibrillation in older subjects.[69]
We screen T1DM patients for dysthyroidism on an annual basis, using TSH, T4 and TPO levels. In case of a suppressed TSH level, TSH receptor antibodies are looked for. General guidelines based on expert opinion for the management of hyperthyroidism have been published by both the American Thyroid Association and the American Association of Clinical Endocrinologists.[70,71]

COELIAC DISEASE

Coeliac disease (CD) is defined as a pertinent intolerance to dietary gluten. In 1888, Samuel Gee first described the clinical features of coeliac sprue.[72] Dicke observed that the ingestion of certain cereal grains, including wheat and rye, was harmful to children with coeliac disease and demonstrated that the alcohol-soluble, or gliadin, component of the water-insoluble protein, or gluten, moiety of wheat produced fat malabsorption in patients with coeliac disease.[73] CD results from a T-lymphocyte-driven autodestructive process within the gastrointestinal mucosa as response to certain dietary cereals.[74,75] CD is characterised by inflammation, villous atrophy and crypt hyperplasia of the small bowel mucosa. These mucosal lesions recover when gluten is withdrawn from the diet. Diagnosis is made by biopsy of the mucosa of the proximal small intestine. Presence of circulating antibodies against gliadin (AGA), endomysium (EmA) and tissue transglutaminase (tTGA) further support diagnosis.[76] These antibodies ultimately disappear in most patients with coeliac disease who follow a gluten-free diet.
Susceptibility to coeliac disease is determined to a significant extent by genetic factors localised within the HLA region. Approximately 90% of coeliac disease patients share the HLA DR3/DQ2 configuration.[77] A weak association between EmA-IgA and HLADQA1*0501-DQB1*0201 has been reported.[4] The prevalence of tTGA has been reported to be as high as 32% in HLA DQ2 homozygous T1DM patients, as compared with 2% in patients without HLA DQ2 or DQ8.[78] The prevalence of HLA DQ2 in the population is 20 to 30% and only a minority of these will ever develop coeliac disease. This implies the involvement of additional, non-HLA linked, genes in the pathogenesis of coeliac disease. MIC-A polymorphisms have been linked to celiac disease, as described above.

The coexistence of T1DM and CD could be explained by the sharing a common genetic factor in the HLA region,[18,19] or by molecular mimicry by which gliadin or tissue transglutaminase activates T cells that are cross-reactive with various autoantigens. During active β-cell destruction, transglutaminase C, which is expressed in pancreatic islets, might be presented in an immunogenic form. In view of the high frequency of coeliac disease in patients with the HLA DQA1*0501-DQB1*0201 haplotype, this presentation may be facilitated by these alleles. Such inflammatory responses may have the capacity to persist in genetically susceptible hosts and lead to chronic organ-specific autoimmune disease.[79] Furthermore, it has been suggested that in the development of autoimmunity in T1DM, the failure to achieve tolerance to autoantigens derives from the gut.[80]

The prevalence of coeliac disease in Western countries is estimated at about 0.5%.[74,75,81] It ranges between 1 to 8% in patients with T1DM (*table 1*).[4,74,82-87] The coexistence of T1DM and CD was first described by Walker-Smith in 1969.[88] About 5% of patients with CD have autoimmune thyroid disease.[74] Conversely, up to 2 to 4% of patients with autoimmune thyroid disease are affected by coeliac disease.

Clinical features of coeliac disease may be subtle and include mild abdominal discomfort and bloating, weight loss, fatigue, but also growth abnormalities mimicking constitutional growth delay, infertility, recurrent aphtous stomatitis, low bone mineralisation and hypocalcaemia with vitamin D deficiency and compensatory hyperparathyroidism, and rarely enteropathy-associated T-cell lymphoma.[74,75,89-91] Iron or folic acid deficiency with or without anaemia is the most common laboratory finding. Hypoglycaemia and a reduction of insulin requirements may indicate the presence of coeliac disease in type 1 diabetes.[82,92] Some report no effect,[84,93] whereas others report improved control with less hypoglycaemic episodes [92,94] after gluten-free diet.

Coeliac disease is considered sufficiently prevalent and the benefits of diagnosis and treatment by gluten withdrawal are such that it is advocated to screen all T1DM patients for this disorder.[82,83] When serological screening is used, most cases of CD will be detected within one year after onset of T1DM.[85] Current (ADA) recommendations for screening subjects with T1DM are to obtain autoantibodies at diagnosis and with symptoms of CD.[64] Barker *et al.* propose measuring tTGA autoantibodies every two years.[2] When positive, subjects should have a small intestinal biopsy to confirm diagnosis. Others advocate that serological screening for coeliac disease in T1DM should be carried out every fifth year due to the possibility of latent coeliac disease, but prospective studies are lacking to substantiate this policy.[85] At this moment there remains controversy as to whether asymptomatic coeliac disease - when detected - should be treated with a gluten-free diet. Large clinical trials are needed to address this question. We suggest to test at onset of T1DM and then yearly for three years, and five yearly thereafter, or at any other time if there are clinical indications, because the test may later become positive.

AUTOIMMUNE GASTRITIS

In 1849, Thomas Addison was the first to report a patient with autoimmune atrophic gastritis.[95] He described a 'very remarkable form of anaemia', which was later called pernicious anaemia that was linked to atrophy of the gastric mucosa. Autoimmune gastritis is characterised by atrophy of corpus and fundus mucosa, and presence of circulating autoantibodies to the parietal cell (PCA) and to their secretory product, intrinsic factor (AIF). PCA and AIF are present in 60 to 85% and 30 to 50% of patients, respectively.[96,97] The prevalence of PCA positivity increases with age: from 2.5% in the third decade to 12% in the eighth decade in the general population.[98,99] In T1DM patients, PCA are found in 10 to 15% of children and in 15 to 25% of adults (*table 1*).[4,6-8,100]

Chronic autoaggression to the gastric proton pump, H^+/K^+ ATPase, may result in decreased gastric acid secretion, hypergastrinaemia, and iron deficiency anaemia.[101,102] In a later stage of the disease, pernicious anaemia results from vitamin B12 deficiency, which is ten times more common in type 1 diabetic than nondiabetic subjects. Finally, in up to 10% of patients, autoimmune gastritis may predispose to gastric carcinoid tumours or adenocarcinomas.[103,104]

Endoscopic features of AIG include a shiny and red mucosa, a thin stomach wall and flattened or absent rugal folds. In biopsy specimens, lymphocytic infiltrates are present in the submucosa and lamina propria. In the next stage, intestinal metaplasia or enterochromaffin-like cell hyperplasia can be seen.

Autoimmune gastritis (AIG) and pernicious anaemia (PA) are common autoimmune diseases with respective prevalences of 2% and 0.15 to 1%, in the general population, increasing with age.[98-100] In patients with T1DM the prevalence is three to fivefold increased with respective frequencies of 5 to 10% and 2 to 4%.[100,104] Pernicious anaemia occurs in 2 to 12% of patients with autoimmune thyroid disease,[105,106] in 6% of those with Addison's disease, in 9% of those with primary hypoparathyroidism, and in 3 to 8% of those with vitiligo (*table 1*).[96] AIG/PA is also part of the autoimmune polyglandular syndrome (APS).[3] Iron deficiency anaemia is present in 20 to 40% of patients with autoimmune gastritis,[101,102] whereas pernicious anaemia can be diagnosed in up to 15 to 25% of patients.[96,97] The progression of AIG to pernicious anaemia is likely to span 20 to 30 years. Finally, gastric carcinoid tumours are

observed in 4 to 9% of patients with AIG/PA, which is 13 times more frequent than in controls.[103,104] Patients with AIG/PA also have a three to sixfold increased gastric cancer risk, ranging from 0.9 to 9%.[103,107]

A genetic predisposition to AIG/PA has been suggested by its familial occurrence.[108] However, the link between AIG/PA and particular HLA haplo/genotypes is weak. In T1DM patients, a weak association between PCA positivity and the HLA DQA1*0501-B1*0301 haplotype, linked to HLA-DR5, has been observed.[62] Patients who manifest both pernicious anaemia and endocrine disease often have a DR3/DR4 genotype.[109] In mouse models, four distinct genetic regions that confer genetic susceptibility to autoimmune gastritis have been identified (Gasa1-4).[110] Three of these four susceptibility loci are nonmajor histocompatibility complex genes that colocalise with those of T1DM.[111,112] This is the strongest concordance identified between any two autoimmune diseases so far. In patients with T1DM, immunological risk factors that have been associated with PCA-positivity include persistent ICA positivity,[4,7,8] GADA positivity,[4,62] and aTPO positivity.[4,62] The association with GADA might be explained by the fact that GAD-65 is not only present in the pancreas and brain but can also be found in the thyroid gland and stomach. PCA are more frequent in type 1 diabetic patients than in their first-degree relatives, even after HLA matching, suggesting that the diabetic condition itself plays an important role.[108] No gender associations were found for PCA. Up to 50% of patients with autoimmune gastritis have aTPOs.[106,108] These results support the recommendation of screening patients with autoimmune thyroid disease for AIG.

Clinical presentation varies widely. Iron deficiency anaemia presents as a hypochromic microcytic anaemia. Symptoms include pallor, fatigue and reduced exercise performance. Patients with pernicious anaemia present with a macrocytic anaemia and a low vitamin B12 which may lead to a painful neuropathy.[96]

Early detection of PCA, AIG and associated pathology is important, not only for prevention of iron deficiency anaemia, but also for prevention of pernicious anaemia which may cause neurological damage and may lead to (pre)malignant gastric lesions. No clear guidelines for the management are available, but we suggest to examine gastrin, iron, vitamin B12 levels and perform a complete blood count at yearly intervals. It seems prudent to test PCA status at the onset of diabetes and then yearly for three years, then five yearly thereafter.[96] Particularly T1DM patients with positive GADA and aTPO should be screened. It is controversial whether patients with AIG/PA should be placed under a surveillance programme with regular gastroscopies. Performing gastroscopy is indicated at least once in patients with PCA positivity, anaemia or high gastrin levels.[96] Since both AIG and pernicious anaemia predispose to gastric carcinoid tumours, which manifest only late in the disease process, a good follow-up is warranted. The possible adverse impact on the health of the patient provides a strong rationale for screening, periodic surveillance by gastroscopy with biopsy, early diagnosis, prevention and/or treatment.[96]

ADDISON'S DISEASE

Addison's disease (AD) is the most frequent cause of primary adrenal insufficiency. It results from destruction of the adrenal cortex with an ensuing deficiency of cortisol, aldosterone, and in females of adrenal androgens.[113] In 1849, Thomas Addison described a group of patients with severe anaemia and coexistent adrenalitis and/or adrenal atrophy and some had coexisting vitiligo.[114] The suprarenal syndrome was named Addison's disease by Wilks in 1862. Primary adrenal insufficiency (Addison's disease) has been reported to affect 1 in 10,000 in the general population.[116]

Autoimmune adrenal insufficiency results from destruction of the adrenal cortex by cytotoxic T lymphocytes.[113] In the active phase of the disease, there is a widespread mononuclear cell infiltrate. There is loss of normal three-layer structure of the adrenal cortex and adrenocortical cells show necrosis and pleiomorphism. The cytochrome P450 enzyme 21-hydroxylase has been identified as a major antigen for the antibodies.[115] Also in AD, screening for 21-hydroxylase antibodies (21-OHAA) identifies subjects who are at risk to develop AD before clinical presentation. Clinical disease can either present as isolated AD or in combination with other autoimmune diseases as part of the 'APS'.[116] In T1DM the prevalence of antiadrenal cortical antibodies (AAA or 21-OH antibodies) ranges between 0.7 to 3%, compared with 0 to 0.6% in first-degree relatives and controls (*table 1*).[4,7,8,115,117-120] A small number of autoantibody-positive subjects have been followed for the development of AD, and a yearly incidence of AD of approximately 20% has been observed.[121] AAA are more frequent in female subjects[7] and in T1DM patients with persisting ICA positivity.[4,7] Furthermore, AD is frequently associated with other autoimmune endocrinopathies, particularly with Hashimoto's thyroiditis (Schmidt's syndrome). Barker *et al.* reported in their patient group that 70% of patients with 21-OHAA also expressed thyroid autoimmunity.[122]

Genetic susceptibility for AD has, not surprisingly, also been linked to the MHC complex on chromosome 6. The HLA DRB1*0404/DQ8-DRB1*0301/DQ2 genotype occurs at an increased frequency in individuals with isolated AD and in those with AD and T1DM.[120] A second locus within the MHC, the MHC class I-related MIC-A, has been

linked to AD.[123] Homozygosity for MICA5.1 (allele 5.1) was associated with an 18-fold increased risk for AD.[124]

Adrenal insufficiency may cause persistent vomiting, anorexia, hypoglycaemia, unexplained weight loss in an adult, malaise, ill-defined fatigue, muscular weakness, hypotension, and craving for salt.[125,126] The most specific sign of primary adrenal insufficiency is generalised hyperpigmentation of the skin and mucosal surfaces, which is due to the high plasma concentrations of melanocyte-stimulating activity of β lipotropin, which derives from the same precursor as ACTH. Laboratory tests can aid in the diagnosis: hyponatraemia, hyperkalaemia, and acidosis. In addition, hypocorticism may, by reducing the insulin needs, cause frequent attacks of hypoglycaemia. Patients with symptomatic adrenal insufficiency should be treated with hydrocortisone and with fludrocortisone as a substitute for aldosterone.[113] Patients with suspected AD and hypothyroidism should be evaluated and treated for adrenal insufficiency prior to replacement of thyroid hormone to avoid an Addisonian crisis, since thyroxine may increase hepatic corticosteroid metabolism.

The natural history of the progression of the disease follows a typical pattern (different stages) which can be correlated to clinical symptoms. One discriminates a potential phase (genetic susceptibility and/or 21-OH antibodies), a latent phase (elevated plasma renin activity (PRA) and normal basal cortisol and ACTH levels), and a clinical phase (a diminished basal cortisol and elevated ACTH concentration).[116] These parameters constitute the endocrine evaluation of adrenal function: PRA, ACTH, cortisol and corticotropin stimulation testing.

The exact frequency of screening for 21-OHAA in individuals with T1DM remains controversial. Screening for 21-OHAA at diagnosis of T1DM and then every two years seems to be a good practice. If autoantibodies are positive, one has to evaluate morning baseline ACTH, cortisol and PRA levels (supine position) and perform a corticotropin stimulation test. However, in the absence of symptoms, an annual basal cortisol and ACTH may be sufficient.[122]

VITILIGO

Vitiligo is an autoimmune-mediated hypomelanotic disorder, with a prevalence of approximately 0.5% in the general population. Half of the patients present with vitiligo before adulthood.[127] Vitiligo is characterised by circumscribed depigmented macules resulting from the loss of epidermal melanocytes. The initial cause is still unclear, but involves immunological factors, oxidative stress, and a sympathetic neurogenic disturbance. Most cases with vitiligo have antibodies against melanocytes.[127,128] In populations of European origin, variants in the gene encoding NACHT leucine-rich-repeat protein-1 (NALP1) have been observed in vitiligo-associated multiple autoimmune diseases.[129] A significant association of allele HLA DR4 and vitiligo has also been reported.[128]

Patients with vitiligo should be asked whether any family member has a history of vitiligo, a thyroid disorder or other autoimmune disease such as T1DM or pernicious anaemia. Also, because vitiligo is associated with an increased risk for Hashimoto's thyroiditis, the TSH level and TPO antibodies should be measured annually. A high index of suspicion for other autoimmune diseases is warranted. Autoimmune thyroiditis, autoimmune gastritis, pernicious anaemia, and T1DM are found more commonly in vitiligo patients compared with the background population, with frequencies of 30, 15, 5, and up to 10%.[130-133]

Treatment of vitiligo may include narrow-band UVB radiation as first-line therapy for widespread disease. In the case of localised disease, a topical corticosteroid or calcineurin inhibitor can be applied. Camouflage techniques can also be useful. Guidelines for the management of vitiligo have been published by the British Association of Dermatologists.[134]

CONCLUSIONS

Type 1 diabetic patients exhibit an increased risk of other autoimmune disorders such as autoimmune thyroid disease, coeliac disease, autoimmune gastritis, Addison's disease, and vitiligo. Approximately 15 to 30% of patients with T1DM have thyroid antibodies, and up to 50% of such patients progress to clinical autoimmune thyroid disease. The prevalence of autoimmune gastritis and pernicious anaemia is 5 to 10% and 2.6 to 4% respectively. Approximately 4% of T1DM patients have concomitant coeliac disease and 0.5% have Addison's disease. Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease. Patients and family members should be educated to be able to recognise signs and symptoms of underlying disease. It is important to keep in mind that genetic background may affect the risk for autoimmune disease, and this may vary dependent on the region where the patient is coming from. A different genetic background may influence the need for and organisation of screening strategies.

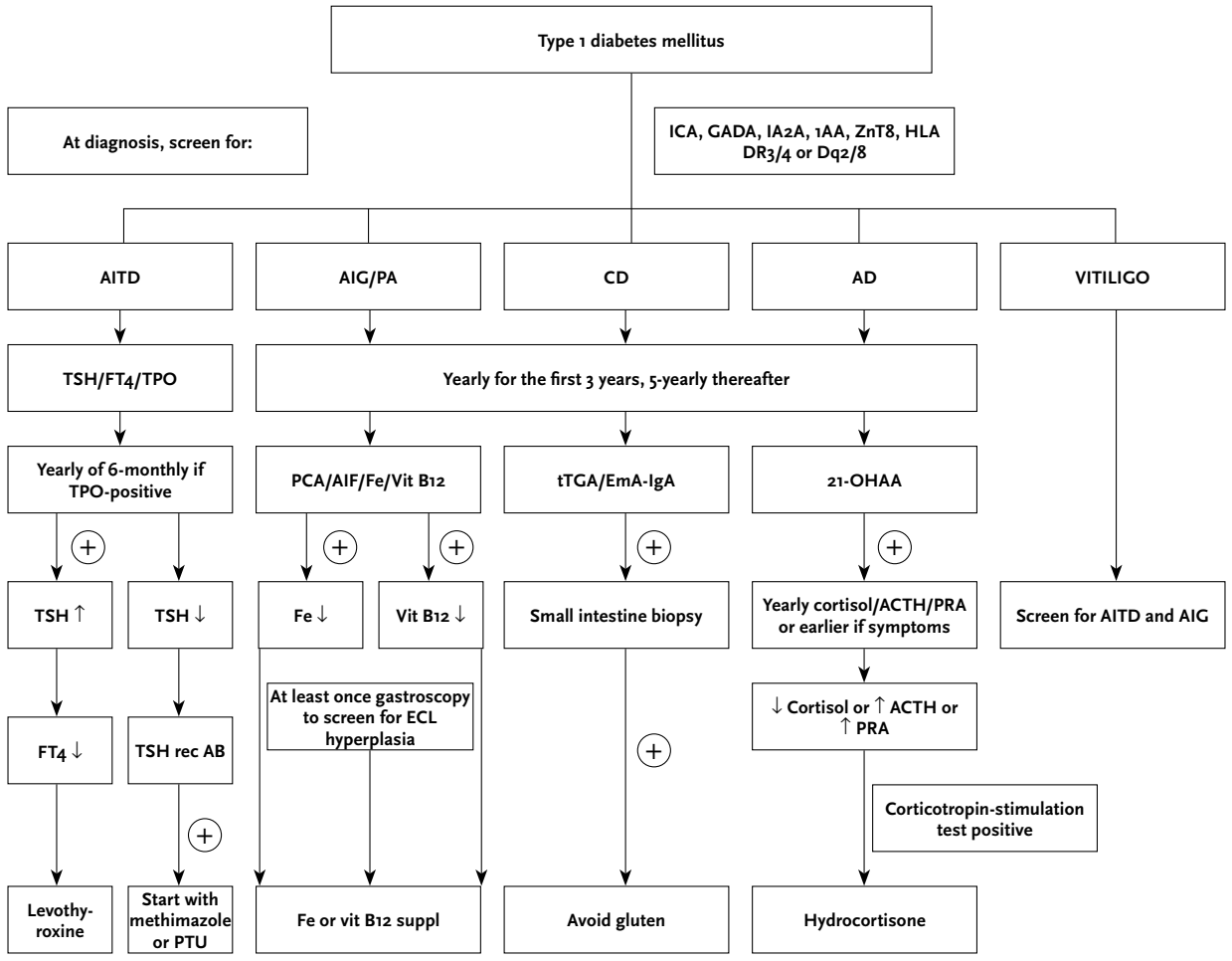
In clinical practice we screen for TPO antibodies, PCA, EmA-IgA and 21-OHAA at diagnosis of T1DM. After diagnosis, regular screening of autoantibodies is warranted (*figure 1*):

- We screen T1DM patients for dysthyroidism on an annual basis, using TSH, T4 and TPO levels. When TPO antibodies are positive and thyroid function is still normal, we screen patients for overt thyroid

dysfunction on a more frequent basis (every 6 months to 1 year). When aTPO are negative, we still test thyroid function on an annual basis. In case of a suppressed TSH level, TSH receptor antibodies are looked for. Clinical signs and symptoms of dysthyroidism warrant earlier testing.

- Due to the possibility of latent coeliac disease, we suggest measuring tTGA and EmA autoantibodies at onset of T1DM and then yearly for three years, and five yearly thereafter, or at any other time if there are clinical indications, because the test may later become positive. When positive, subjects should have a small intestinal biopsy to confirm diagnosis. Clinical suspicion should be high in case of growth failure or delayed puberty in children, osteopenia, anaemia, menstrual irregularity, and glycaemic instability.
- Testing PCA status yearly after T1DM onset is recommended for three years, then five yearly thereafter. Particularly those patients with positive GADA and aTPO should be screened. We also examine gastrin, iron, and vitamin B12 levels and perform a complete blood count at yearly intervals. Performing gastroscopy is indicated in patients with PCA positivity, anaemia or high gastrin levels.
- For Addison's disease, in line with our screening procedure for other autoimmune disorders, we screen for 21-OHAA at onset and yearly for three years, then five-yearly thereafter, or in case of clinical suspicion. If autoantibodies are positive, an annual check-up of basal cortisol and ACTH (at minimum) should be performed. Clinical suspicion is warranted in case of unexplained weight loss, refractory hypoglycaemia, hyperpigmentation or unexplained hypotension.

Figure 1. *Flowchart for screening and follow-up of associated autoimmune disorders in patients with T1DM*



AB = antibody; AD = Addison's disease; AIF = antibodies to intrinsic factor; AITD = autoimmune thyroid disease; AIG = autoimmune gastritis; CD = coeliac disease; ECL = endocrine cell hyperplasia; EmA-IgA = anti-endomysium antibodies; IAA = insulin autoantibodies; ICA = islet cell antibodies; FT4 = free T4; GADA = glutamic acid decarboxylase-65 antibodies; PA = pernicious anaemia; PCA = parietal cell antibodies; PRA = plasma renin activity; PTU = propylthioluracil; TPO = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone; tTGA = tissue transglutaminase antibodies; 21-OHAA = 21-hydroxylase antibodies.

NOTE

Part of the studies mentioned and performed by the authors were supported by a grant from the European Foundation for the Study of Diabetes (EFSD).

REFERENCES

1. Eisenbarth GS. Type 1 diabetes mellitus - a chronic autoimmune disease. N Engl J Med. 1986;314:1360-8.
2. Barker JM. Clinical review: Type 1 diabetes associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006;91:1210-7.
3. Eisenbarth GS, Gottlieb PA. Autoimmune Polyendocrine Syndromes. N Engl J Med. 2004;350:2068-79.
4. De Block C, De Leeuw I, Vertommen J, et al. The Belgian Diabetes Registry. β-cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. Clin Exp Immunol. 2001;126:236-41.
5. Barker JM, Yu J, Yu L, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. Diabetes Care. 2005;28:850-5.
6. Landin-Olsson M, Karlsson FA, Lernmark A, Sundkvist G. Diabetes Incidence Study in Sweden Group. Islet cell and thyrogastric antibodies in 633 consecutive 15- to 34-yr-old patients in the Diabetes Incidence Study in Sweden. Diabetes. 1992;41:1022-7.
7. Maclaren NK, Riley WJ. Thyroid, gastric, and adrenal autoimmunities associated with insulin-dependent diabetes mellitus. Diabetes Care. 1985;8(Suppl.):34-8.
8. Betterle C, Zanette F, Pedini B, et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. Diabetologia. 1984; 26:431-6.
9. Nepom GT, Kwok WW. Molecular basis for HLA-DQ associations with IDDM. Diabetes. 1998;47:1177-84.
10. Jacobson EM, Huber A, Tomer Y. The HLA gene complex in thyroid autoimmunity: from epidemiology to etiology. J Autoimmun. 2008;30:58-62.
11. Eisenbarth GS. Update in Diabetes. J Clin Endocrinol Metab. 2007;92:2403-7.
12. Caillat-Zucman S. Molecular mechanisms of HLA association with autoimmune diseases. Tissue Antigens. 2009;73:1-8.
13. Ueda H, Howson JM, Esposito L, et al. Association of the T-cell regulatory gene CTLA-4 with susceptibility to autoimmune disease. Nature. 2003;423:506-11.
14. Vaidya B, Pearce S. The emerging role of the CTLA-4 gene in autoimmune endocrinopathies. Eur J Endocrinol. 2004;150:619-26.
15. Hue S, Monteiro RC, Berrih-Aknin S, Caillat-Zucman S. Potential role of NKG2D/MHC class I-related chain A interaction in intrathymic maturation of single-positive CD8 T cells. J Immunol. 2003;171:1909-17.
16. Caillat-Zucman S. How NKG2D ligands trigger autoimmunity? Hum Immunol. 2006;67:204-7.
17. Gambelunghe G, Ghaderi M, Cosentino A, et al. Association of MHC class I chain-related A (MIC-A) gene polymorphism with type 1 diabetes. Diabetologia. 2000;43:507-14.
18. Bilbao JR, Martin-Pagola A, Vitoria JC, Zubillaga P, Ortiz L, Castano L. HLA-DRB1 and MHC class 1 chain-related A haplotypes in Basque families with celiac disease. Tissue Antigens. 2002;60:71-6.
19. Lopez-Vazquez A, Rodrigo L, Fuentes D, et al. MHC class I chain related gene A (MICA) modulates the development of coeliac disease in patients with the high risk heterodimer DQA1*0501/DQB1*0201. Gut. 2002;50:336-40.
20. Barker JM, Ide A, Hostetler C, et al. Endocrine and immunogenetic testing in individuals with type 1 diabetes and 21-hydroxylase autoantibodies: Addison's disease in a high risk population. J Clin Endocrinol Metab. 2005;90:128-34.
21. Bottini N, Muscumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nat Genet. 2004;36:337-8.
22. Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. Diabetes. 2004;53:3020-3.
23. Velaga MR, Wilson V, Jennings CE, et al. The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. J Clin Endocrinol Metab. 2004;89:5862-5.
24. Schmidt MB. Eine biglanduläre Erkrankung (Nebeniere und Schilddrüse) bei morbus Addisonii. Verhandlungen der Deutschen Pathologischen Gesellschaft. 1926;21:212-5.
25. Neufeld M, Maclaren NK, Blizzard RM. Autoimmune polyglandular syndromes. Pediatric Annals. 1980;9:154-62.
26. Aaltonen J, Bjorses P, Sandkuijl L, Perheentupa J, Peltonen L. An autosomal locus causing autoimmune disease: autoimmune polyglandular disease type 1 assigned to chromosome 21. Nat Genet. 1994;8:83-7.
27. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001;358:221-9.
28. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes. 1965;14:619-33.
29. Wenzlau JM, Juhl K, Yu L, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. Proc Natl Acad Sci USA. 2007;104:17040-5.
30. Lampeter EF, Homberg M, Quabeck K, et al. Transfer of insulin-dependent diabetes between HLA-identical siblings by bone marrow transplantation. Lancet. 1993;341:1243-5.
31. Yu L, Rewers M, Gianani R, et al. Antiislet autoantibodies usually develop sequentially rather than simultaneously. J Clin Endocinol Metab. 1996; 81:4264-7.
32. Ziegler AG, Hummel M, Schenker M, Bonifacio E. Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes. The 2-year analysis of the German BABYDIAB study. Diabetes. 1999;48:460-8.
33. Kukko M, Kimpimaki T, Korhonen S, et al. Dynamics of diabetes-associated autoantibodies in young children with human leucocyte antigen-conferred risk of type 1 diabetes recruited from the general population. J Clin Endocrinol Metab. 2005;90:2712-7.
34. Tuomi T, Bjorses P, Falorni A, et al. Antibodies to glutamic acid decarboxylase and insulin-dependent diabetes in patients with autoimmune polyendocrine syndrome type I. J Clin Endocrinol Metab. 1996;81:1488-94.
35. Bingley PJ, Bonifacio E, Williams AJK, Genovese S, Bottazzo GF, Gale EAM. Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes. 1997;46:1701-10.
36. Decochez K, de Leeuw IH, Keymeulen B, et al. IA-2 autoantibodies predict impending type I diabetes in siblings of patients. Diabetologia. 2002;45:1658-66.
37. Todd JA, Bell JI, McDevitt HO. HLA DQβ-gene contributes to susceptibility and resistance to insulin-dependent diabetic individuals. Nature. 1987;329:599-604.
38. Bell GI, Horita S, Karam JH. A polymorphic locus of the human insulin gene is associated with insulin-dependent diabetes mellitus. Diabetes. 1984;33:176-83.
39. Van der Auwera BJ, Heimberg H, Schrevens AF, Van Waeyenberge C, Flament J, Schuit FC. 5' Insulin gene polymorphism confers risk to IDDM independently of HLA class II susceptibility. Diabetes. 1993;42:851-4.
40. Davies JL, Kawaguchi Y, Bennett ST, et al. A genome-wide search for human type I susceptibility genes. Nature. 1994;371:130-6.
41. Nistico L, Buzzetti R, Pritchard LE, et al. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with type 1 diabetes. Hum Mol Genet. 1996;5:1075-80.
42. Baisch JM, Weeks T, Giles R, Hoover M, Stastny P, Capra JD. Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. N Engl J Med. 1990;322:1836-41.

43. Baisch JM, Weeks T, Giles R, Hoover M, Stastny P, Capra JD. Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. N Engl J Med. 1990;322:1836-41.

44. Heimberg H, Nagy ZP, Somers G, de Leeuw I, Schuit FC. Complementation of HLA DQA and DQB genes confers susceptibility and protection to insulin-dependent diabetes mellitus. Hum Immunol. 1992;33:10-7.

45. Thorsby E, Ronningen KS. Particular HLA-DQ molecules play a dominant role in determining susceptibility or resistance to type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1993;36:371-7.

46. Bingley PJ, Colman P, Eisenbarth GS, et al. Standardization of IVGTT to predict IDDM. Diabetes Care. 1992;15:1313-6.

47. Chase HP, Dolan LM, Krischer JP, et al. First phase insulin response in young healthy children during the intravenous glucose tolerance test as a risk factor for type 1 diabetes. J Pediatr. 2001;138:244-9.

48. Meier J, Bhushan A, Butler AE, Rizza RA, Butler PC. Sustained β cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration? Diabetologia. 2005;48:2221-8.

49. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med. 2005;352:2598-608.

50. Vandemeulebroucke E, Keymeulen B, Decochez K, et al. Hyperglycemic clamp test for diabetes risk assessment in IA-2 antibody-positive relatives of type 1 diabetic patients. Diabetologia. 2009;in press.

51. Hashimoto H. Zur kenntnis der lymphomatosen veranderung der schilddruse (struma lymphomatosa). Acta Klin Chir. 1912;97: 219-48.

52. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003;348:2646-55.

53. Vanderpump MPJ, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. Clin Endocrinol. 1995;43:55-68.

54. Riley WJ, maclaren NK, Lezotta DC, Spillar RP, Rosenbloom AL. Thyroid autoimmunity in insulin-dependent diabetes mellitus: the case for routine screening. J Pediatr. 1981;98:350-4.

55. Kontiainen S, Schlenzka A, Koskimies S, Rilva A, Maenpaa J. Autoantibodies and autoimmune diseases in young diabetics. Diabetes Res. 1990;13:151-6.

56. Kordonouri O, Klinghammer A, Lang EB, Gruters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care. 2002;25:1346-50.

57. Kim EY, Shin CH, Yang SW. Polymorphisms of HLA class II predispose children and adolescents with type 1 diabetes to autoimmune thyroid disease. Autoimmunity. 2003;36:177-81.

58. Perros P, McCrimmon RJ, Shax G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet Med. 1995;12:622-7.

59. Umpierrez GE, Latif KA, Murphy MB, et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care. 2003;26:1181-5.

60. Kawasaki E, Takino H, Yano M, et al. Autoantibodies to glutamic acid decarboxylase in patients with IDDM and autoimmune thyroid disease. Diabetes. 1994;43:80-6.

61. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet. 1974;ii:1279-82.

62. De Block CE, de Leeuw IH, Rooman RP, Winnock F, Du Caju MV, van Gaal LF. Gastric parietal cell antibodies are associated with glutamic acid decarboxylase-65 antibodies and the HLA DQA1*0501-DQB1*0301 haplotype in type 1 diabetes mellitus. Belgian Diabetes Registry. Diabet Med. 2000;17:618-22.

63. Barbesino G, Chiovato L. The genetics of Hashimoto's disease. Endocrinol Metab Clin North Am. 2000;29:357-73.

64. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28:186-212.

65. Graves RJ. Newly observed affection of the thyroid gland in females. Lond Med Surg J. 1835;7:517.

66. Brent GA. Graves' disease. N Engl J Med. 2008;358:2594-605.

67. Gough SCL. The genetics of Graves' disease. Endocrinol Metab Clin North Am. 2000;29:255-66.

68. Santamaria P, Barbosa JJ, Lindstrom AL, Lemke TA, Goetz FC, Rich SS. HLA-DQB1-associated susceptibility that distinguishes Hashimoto's thyroiditis from Graves' disease in type 1 diabetic patients. J Clin Endocrinol Metab. 1994;78:878-83.

69. Toft AD. Subclinical hyperthyroidism. N Engl J Med. 2001;345:512-6.

70. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA. 1995;273:808-12.

71. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002;8:457-69.

72. Gee S. On the coeliac affection. St Barth Hosp Rep. 1888;24:17-20.

73. Dicke WK, Weijers HA, van de Kamer JH. Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. Acta Paediatr Scand. 1953;42:34-42.

74. Collin P, Kaukinen K, Valimaki M, Salmi J. Endocrinological disorders and celiac disease. Endocrine Rev. 2002;23(4):464-83.

75. Green PH, Cellier C. Celiac disease. N Engl J Med. 2007;357:1731-43.

76. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3:797-801.

77. Sollid LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for a primary association of celiac disease to a particular HLA-DQ α/βheterodimer. J Exp Med. 1989;169:345-50.

78. Bao F, Yu L, Babu S, et al. One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase antibodies. J Autoimmun. 1999;13:143-8.

79. Schuppan D. Current concepts of celiac disease pathogenesis. Gastroenterology. 2000;119:234-42.

80. Paronen J, Klemetti P, Kantele JM, et al. Glutamate decarboxylase-reactive peripheral blood lymphocytes from patients with IDDM express gut-specific homing receptor α4β7-integrin. Diabetes. 1997;46:583-8.

81. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology. 2001;120:636-51.

82. Cronin CC, Shanahan F. Insulin-dependent diabetes mellitus and coeliac disease. Lancet. 1997;349:1096-7.

83. Holmes GKT. Coeliac disease and type 1 diabetes mellitus - the case for screening. Diabet Med. 2001;18:169-77.

84. Sategna-Guidetti C, Grosso S, Pulitano R, Benaduce E, Dani F, Carta Q. Celiac disease and insulin-dependent diabetes mellitus, screening in an adult population. Dig Dis Sci. 1994;39:1633-7.

85. Saukonen T, Savilahti E, Reijonen H, Ilonen J, Tuomilehto-Wolf E, Akerblom HK. Coeliac disease: frequent occurence after clinical onset of insulin-dependent diabetes mellitus. Diabet Med. 1996;13:464-70.

86. Kordonouri O, Dieterich W, Schuppan D, et al. Autoantibodies to tissue transglutaminase are sensitive serological parameters for detecting silent coeliac disease in patients with type 1 diabetes mellitus. Diabet Med. 2000;17:441-4.

87. Lampasona V, Bonfanti R, Bazzigaluppi E, et al. Antibodies to tissue transglutaminase C in type I diabetes. Diabetologia. 1999;42:1195-8.

88. Walker-Smith JA, Grigor W. Coeliac disease in a diabetic child. Lancet. 1969;i:1021.

89. Hoffenberg EJ, Fallstrom SP, Jansson G, Jansson U, Lindberg T. Clinical features of children with screening-identified evidence of celiac disease. Pediatrics. 2004;113:1254-9.

90. Collin P, Vilska S, Heinonen PK, Hallstrom O, Pikkarainen P. Infertility and coeliac disease. Gut. 1996;46:332-5.

91. Nuti R, Martini G, Valenti R, Giovani S, Salvadori S, Avantzati A. Prevalence of undiagnosed coeliac syndrome in osteoporotic women. J Intern Med. 2001;250:361-6.

92. Iafusco D, Rea F, Prisco F. Hypoglycemia and reduction of insulin requirement as a sign of coeliac disease in children with IDDM. Diabetes Care. 1998;21:1379-80.

93. Kaukinen K, Salmi J, Lahtela J, et al. No effect of gluten-free diet on the metabolic control of type 1 diabetes in patients with diabetes and coeliac disease. Diabetes Care. 1999;22:1747-8.

94. Andreelli F, Plotton I, Riou JP, Thivolet C. Diabetic instability and coeliac disease. Diabetes Care. 1998;21:2192-3.

95. Addison T. Anaemia: disease of suprerenal capsules. London Med Gae. 1849;8:517-8.

96. De Block C, de Leeuw I, van Gaal L. Autoimmune gastritis in type 1 diabetes: a clinically oriented review. J Clin Endocrinol Metab. 2008;93:363-71.

97. Toh BH, Van Driel IR, Gleeson PA. Mechanisms of disease: pernicious anemia. N Engl J Med. 1997;337:1441-8.

98. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997;84:223-43.

99. Carmel R. Prevalence of undiagnosed pernicious anemia in the elderly. Arch Intern Med. 1996;156:1097-100.

100. De Block C, Van Gaal L, Leeuw I, Belgian Diabetes Registry. High prevalence of manifestations of gastric autoimmunity in parietal cell-antibody positive type 1 (insulin-dependent) diabetic patients. J Clin Endocrinol Metab. 1999;84:4062-7.

101. Marignani M, Delle Fave G, Mecarocci S, et al. High prevalence of atrophic body gastritis in patients with unexplained microcytic and macrocytic anemia. Am J Gastroenterol. 1999;94:766-72.

102. De Block CE, van Campenhout CM, de Leeuw IH, et al. Soluble transferrin receptor level: a new marker of iron deficiency anemia, a common manifestation of gastric autoimmunity in type 1 diabetes. Diabetes Care. 2000;23:1384-8.

103. Kokkola A, Sjöblom SM, Haapiainen R, Sipponen P, Puolakkainen P, Jarvinen H. The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia: a prospective follow-up study. Scand J Gastroenterol. 1998;33:88-92.

104. De Block C, de Leeuw I, Bogers J, et al. Autoimmune gastropathy in type 1 diabetic patients with parietal cell antibodies: histological and clinical findings. Diabetes Care. 2003;26:82-8.

105. Doniach D, Roitt IM, Taylor KB. Autoimmune phenomena in pernicious anemia: serological overlap with thyroiditis, thyrotoxicosis and systemic lupus erythematosus. BMJ. 1963;1:1374-9.

106. Centanni M, Marignani M, Gargano L, et al. Atrophic body gastritis in patients with autoimmune thyroid disease. An underdiagnosed association. Arch Intern Med. 1999;159:1726-30.

107. Hsing A, Hansson L, McLaughlin J, Nyren O, Blot W, Ekbom A, Fraumeni JF Jr. Pernicious anemia and subsequent cancer: a population-based cohort study. Cancer. 1993;71:745-50.

108. De Block CE, de Leeuw IH, Decochez K, et al. The presence of thyrogastric antibodies in first-degree relatives of type 1 diabetic patients is associated with age and proband antibody status. J Clin Endocrinol Metab. 2001;86:4358-63.

109. Ungar B, Mathews J, Tait BD, Cowling DC. HLA-DR patterns in pernicious anemia. BMJ (Clin Res Ed). 1981;282:768-70.

110. Baxter AG, Jordan MA, Silveira PA, Wilson WE, van Driel IR. Genetic control of susceptibility to autoimmune gastritis. Int Rev Immunol. 2005;24:55-62.

111. Van Driel IR, Baxter AG, Laurie KL, et al. Immunopathogenesis, loss of T cell tolerance and genetics of autoimmune gastritis. Autoimmun Rev. 2002;1:290-7.

112. Van Driel IR, Read S, Zwar T, Gleeson PA. Shaping the T cell repertoire to a bona fide autoantigen: lessons from autoimmune gastritis. Curr Opin Immunol. 2005;17:270-6.

113. Ten S, New M, Maclaren N. Addison's disease. J Clin Endocrinol Metab. 2001;86:2909-22.

114. Addison T. On the constitutional and local effects of disease of the suprarenal capsules. In a collection of the published writing of the late Thomas Addison, M.D., physician to Guy's Hospital London: New Sydenham Society, 1868 (reprinted in Medical Classics 1937; 2:244-293).

115. Winqvist O, Karlsson FA, Kampe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. Lancet. 1992;339:1559-62.

116. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocrine Rev. 2002;23(3):327-64.

117. Anderson JR, Goudie RB, Gray KG, Timbury GC. Autoantibodies in Addison's disease. Lancet. 1957;1:1123-4.

118. Brewer KW, Parziale VS, Eisenbarth GS. Screening patients with insulin-dependent diabetes mellitus for adrenal insufficiency. N Eng J Med. 1997;337:202.

119. Peterson P, Salmi H, Hyoty H, et al. Steroid 21-hydroxylase autoantibodies in insulin-dependent diabetes mellitus. Childhood diabetes in Finland (DiMe) Study Group. Clin Immunopathol. 1997;82:37-42.

120. Yu L, Brewer KW, Gates S, et al. DRB1*04 and DQ alleles: expression of 21-hydroxylase autoantibodies and risk of progression to Addison's disease. J Clin Endocrinol Metab. 1999;84:328-35.

121. Betterle C, Scalici C, Presotto F, et al. The natural history of adrenal function in autoimmune patients with adrenal autoantibodies. J Endocrinol. 1988;117:467-75.

122. Barker JM, Ide A, Hostetler C, et al. Endocrine and immunogenetic testing in individuals with type 1 diabetes and 21-hydroxylase autoantibodies: Addison's disease in a high-risk population. J Clin Endocrinol Metab. 2005;90:128-34.

123. Park YS, Sanjeevi CB, Robles D, et al. Additional assocation of intra-MHC genes, MICA and D6S273, with Addison's disease. Tissue Antigens. 2002;60:155-63.

124. Gambelunghe G, Falorni A, Ghaderi M, et al. Microsatellite polymorphism of the MHC class I chain-related (mic-a and mic-b) genes marks the risk for autoimmune Addison's disease. J Clin Endocrinol Metab. 1999;84:3701-7.

125. Salvatori R. Adrenal insufficiency. JAMA. 2005;294:2481-8.

126. Oelkers W. Adrenal insufficiency. N Engl J Med. 1996;335:1206-12.

127. Taïeb A, Picardo M. Vitiligo. N Engl J Med. 2009;360:160-9.

128. Kemp EH, Waterman EA, Weetman AP. Autoimmune aspects of vitiligo. Autoimmunity. 2001;34:65-77.

129. Jin Y, Mailloux CM, Gowan K, et al. NALP1 in vitiligo-associated multiple autoimmune disease. N Engl J Med. 2007;356:1216-25.

130. Kakourou T, Kanaka-Gantenbein C, Papadopoulou A, Kaloumenou E, Chrousos GP. Increased prevalence of chronic autoimmune (Hashimoto's) thyroiditis in children and adolescents with vitiligo. J Am Acad Dermatol. 2005;53:220-3.

131. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16:208-14.

132. Betterle C, Caretto A, de Zio A, et al. Incidence and significance of organ-specific autoimmune disorders (clinical, latent or only autoantibodies) in patients with vitiligo. Dermatologica. 1985;171:419-23.

133. Amerio P, Tracanna M, De Remigis P, et al. Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3B+C and 4. Clin Exp Dermatol. 2006;31:746-9.

134. Gawkrodger DJ, Ormerod AD, Shaw L, et al. Guideline for the diagnosis and management of vitiligo. Br J Dermatol. 2008;159:1051-76.