The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Diabetes mellitus type 1

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1 Introduction

Type 1 diabetes mellitus (T1D) is, in the majority of cases, an autoimmune disease caused by the cell-mediated destruction of insulin-producing pancreatic islet cells. Despite the central pathogenic role of T-cells, autoantibodies, as secreted by auto-reactive plasma cells, are diagnostic indicators of immune processes [1]. In rare cases, especially in non-Caucasian populations, a subtype of T1D without any evidence of autoimmunity can be observed (classification as "Type 1 idiopathic" according to WHO).

In contrast to Type 2 diabetes, which is the result of insulin resistance and decreasing β-cell function, more affecting adults and the elderly, T1D starts suddenly with acute symptoms, mostly in childhood and adolescence. A special form of T1D is the slowly progressive Latent Autoimmune Diabetes in Adults (LADA), starting after the 30^{th} to 40^{th} year of age and where symptoms are of intermediate seriousness, mimicking Type 2 diabetes.

In T1D, immune reactions reduce the number of insulin producing beta cells in the islets of Langerhans (Fig. 1). Since glucose uptake in many tissues depends on insulin, the absolute lack of insulin is responsible for increasing blood glucose values and lipolysis. This results in symptoms caused by the high concentration of blood glucose, insufficient utilization of glucose and accumulation of lipolytic products (ketone bodies) (Table 1).

The incidence of T1D has been rising from 9 to 16/100 000 over the last 20 years. The prevalence has increased to 0.8 % in recent decades and differs regionally and socially. Men and women are equally affected.

2 Diagnostic measurements for experts

T1D is an autoimmune disease with a clear genetic background (e. g. HLA-DQ/DR, IDDM2, PTPN22), however, the concordance rate in identical twins is less than 50 %. Despite some clinical, epidemiological and pathological data, there is no clear evidence for a defined viral trigger. Early metabolic signs of the ongoing process

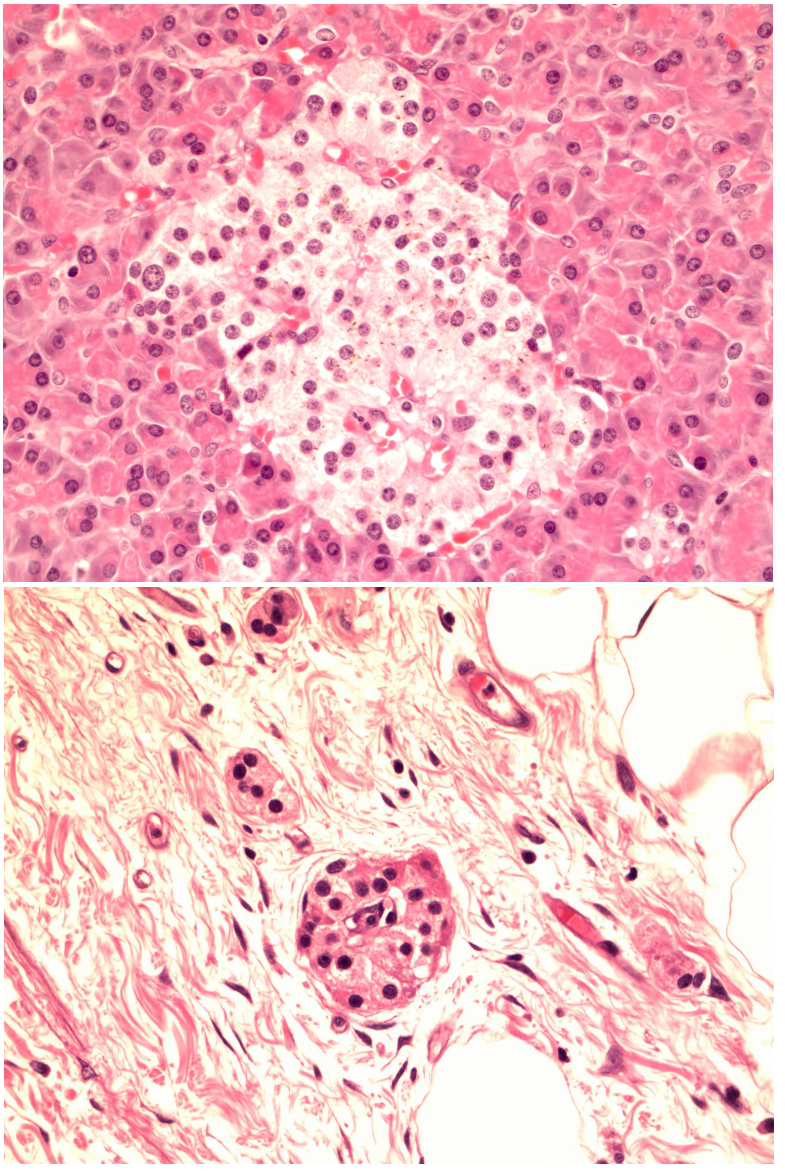

Figure 1. Histopathological pancreas specimen of a healthy (a) and a diabetic (b) person. In a healthy pancreas, islets are formed by bright cells with regular size and shape. Under diabetic conditions, small islets are surrounded by fibrous connective tissue. HE staining, magnification 140 ×.

Table 1. Symptoms of disease.

Acute onset	
high blood glucose concentration	polyuria
	polydipsia
	blurred vision
insufficient utilization of glucose	weight loss
	impaired wound repair
	fatigue
	loss of performance
acute complications	diabetic ketoacidosis
	hypoglycaemia (under treatment)
Chronic disease	
	neuropathy
	nephropathy
	retinopathy
	cardiovascular disease

of β-cell destruction are the loss of the oscillatory pattern of insulin secretion, followed by a missing first phase insulin response after iv glucose stimulation.

It is possible to identify humans with a high risk for T1D by combining family history, other risk factors, antibody screening and repeated metabolic testing. Since no approved preventative therapy is available, screening is recommended only in the setting of clinical trials.

Sometimes associated autoimmune diseases such as thyroiditis, coeliac disease, Addison's disease, or autoimmune polyglandular syndromes facilitate early diagnosis.

In most cases, it is clinical symptoms which will promote further diagnostic evaluation. Diagnosis of diabetes mellitus is confirmed by blood glucose testing (usually either fasting or random, in rare cases after oral glucose load). Metabolic acidosis and ketonuria are indicative for T1D. Insulin, proinsulin, and C-peptide concentrations will be very low, however their estimation is of limited value.

The detection of autoantibodies is a typical laboratory finding in T1D (Table 2). Detection of autoantibodies to islet cell-related antigens is a hallmark of T1D confirmation, but can also be used as an early indicator of diabetic risk. Specificity depends on the quality and characteristics of tests applied in the diagnostic laboratory.

– Islet cell antibodies (ICA) are detected by indirect immunofluorescence on unfixed cryostat sections of human pancreas. They represent the most general in-

Table 2. Diagnostic criteria.

Clinical findings	
	Not defined
Laboratory findings	
Clinical chemistry	Plasma glucose ≥ 11.1 mmol/l (≥200 mg/dl)
	Fasting plasma glucose ≥ 7 mmol/l (≥123 mg/dl)
	Oral glucose tolerance test: ≥ 11.1 mmol/l (≥200 mg/dl) after 2 h
	Ketoacidosis
	Insulin, Proinsulin, C-peptide
	HbA1c (in follow-up)
Immunology	Islet cell antibodies (ICA)
	GAD antibodies
	IA2 antibodies
	Insulin antibodies
	ZnT8 antibodies
	not yet available: islet-specific T cells

Abbreviations: **HbA1c**, glycated haemoglobin; **GAD**, glutamate decarboxylase; **IA2**, insulinoma associated antigen; **ZnT8**, Zinc transporter 8

dicator as they are directed against several autoantigens of pancreatic endocrine cells such as glutamate decarboxylase (GAD) and the tyrosine phosphatase, IA2.

- GAD autoantibodies (GADA) in the sera of T1D patients specifically bind the isozyme GAD65 of the enzyme glutamate decarboxylase. They are analysed by radioimmunoassay (RIA) or enzyme immunoassays (EIA) using recombinant or highly purified native GAD65 as the test antigen. The results obtained with latest generation EIAs are comparable with those of RIAs.
- IA2 (the so called insulinoma associated antigen), a pancreas-specific tyrosine phosphatase, is the second main target of autoantibodies in T1D, detectable by RIA or EIA.
- Insulin autoantibodies (IAA) are detectable by RIA or EIA and are often found as the first T1D-specific autoantibody during disease development, especially in children. Other types of insulin antibodies may be induced by insulin therapy.
- ZnT8 antibodies are directed against the cationic efflux transporter protein Zinc T8. These antibodies seem to be the most specific ones for T1D and can also be found in patients without ICA, GADA, IAA or IA2 antibodies [2].
- Insulin receptor autoantibodies can be found in diabetes of different types. They can induce symptoms of insulin resistance (type B Insulin resistance) or hypoglycaemia. They may indicate a different type of autoimmune diabetes (type 3G) associated with systemic autoimmune diseases (mainly Systemic Lupus Erythe-

matosus) or paraneoplastic syndromes [3]. They are important in differential diagnosis.

Islet cell destruction is dominated by cytotoxic T cells. Although detection of such autoreactive cells can be done experimentally, it is not yet a routine method.

Indications for autoantibody assessment are risk estimation in healthy probands and confirmation of the autoimmune pathogenesis of Type1 diabetes and differential diagnosis of Maturity Onset Diabetes of the Young (MODY) and LADA in cases of overt diabetes. This latter is important since up to 10 % of patients classified as Type 2 diabetes actually have Type 1 diabetes of the LADA-type.

Finally, once T1D is diagnosed, the possible association with other autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, coeliac disease, Addison's disease or autoimmune polyendocrine syndromes should be excluded [4].

3 Requirements for family practitioners

The preclinical period of T1D is mostly invisible, but clinical presentation starts when insulin production is no longer sufficient and metabolic complications occur.

Type 1 diabetes can be an acute disease with presentations including abdominal pain, nausea, pseudoperitonitis shock and coma, and it requires immediate therapy. Without insulin therapy, the progress of T1D is rapid and life-threatening. As well as acute symptoms, longstanding hyperglycaemia induces a large number of chronic complications (Table 1).

In families with a high genetic burden of T1D, screening for relevant autoantibodies can help to detect the disease in relatives as early as possible.

Typically, patients contact their general practitioner with rather general symptoms such as polyuria, polydipsia, weakness, weight loss, blurred vision and infections. In a reasonable number of cases, severe metabolic ketoacidosis can be the initial event. Determination of glucose levels is the first and most relevant laboratory test.

When the diagnosis is suspected, first measures must be directed at preventing life-threatening complications and include fluid, electrolyte and insulin substitution. Next, the patient should be referred to a specialised diabetologist for further examination and laboratory testing. After starting regular sc insulin replacement therapy with an intensified insulin regimen, the patient should return for a continued supervision program.

4 Follow up

Clinical observations

The goal of insulin therapy is to normalise all acute symptoms and signs (Fig. 2).

Figure 2. T1D patient before and under insulin therapy.
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Expectations

T1D is a chronic disease, the prognosis for which depends on the success of maintaining a normal carbohydrate metabolism and avoiding high glucose peak concentrations and hypoglycaemia. Long-term prognosis depends on the development or prevention of secondary complications, i. e. nephropathy, neuropathy, retinopathy, and angiopathy (Table 1).

Blood tests

The success of insulin replacement therapy can be monitored by repeated blood glucose testing (self monitoring). Continuous glucose monitoring is now technically possible but is not yet part of routine care. Measurement of HbA1c allows assessment of intermediate-term stability (3 month period) of glucose metabolism.

5 Management

The treatment must be individualised according to the severity of disease, the patient's wishes and the presence of associated diseases. All patients with Type1 diabetes should participate in structured training and teaching programs.

1. Insulin replacement therapy is the only routinely applied therapeutic approach. This can be done with intensified conventional insulin injections using short

and long acting insulin preparations or insulin pumps (continuous subcutaneous insulin infusion — (CSII) using short acting insulin). Closed loop systems are under development.
2. Pancreas transplantation: Due to the side effects of immunosuppressive therapy, pancreas transplantation is not a routine procedure; it is mostly performed in combination with renal transplantation in cases of renal failure. Severe cases of neuropathic complications with repeated hypoglycaemia are also an indication.
3. Islet and islet cell transfer: Transfer of human islets or islet cells has been under investigation for years. At present, it is not a real therapeutic option.
4. Immunosuppressive treatment: A lot of immunosuppressive and immunomodulating protocols have been tested during the last 30 years and are still under investigation. Due to the side effects and the lack of long-standing islet cell protection, there is, as yet, no approved immunosuppressive therapy for T1D.

6 Diagnostic tests

Laboratory tests for T1D can be divided in two groups: clinical chemistry and immunology.

For detection of blood sugar, HbA1c, insulin, and further parameters relevant for differential diagnosis, clinical chemistry offers standardised test systems.

This is also true for autoantibody detection in immunological labs. To detect the antibodies mentioned above, several methods can be applied. The indirect immunofluorescence test for detection of ICA is a well-established method, standardised by international collaboration. For all singular autoantibodies, there are commercially available, immune-binding assays using recombinant or purified native proteins as antigens. Although RIAs have several advantages, non-radioactive tests are becoming more and more common in diagnostic labs. Different test formats are found at manufacturers' homepages.

7 Testing methods

The benefits and usefulness of the diagnostic laboratory tests are related to their specificities and sensitivities [5]:

- **ICA** are detected with a diagnostic sensitivity at the time of T1D clinical manifestation in 80–90 % of children and 70–80 % of adults. ICA can be found also in up to 40 % of patients with LADA and in 5–10 % of patients with gestational diabetes. Over the course of the disease, the frequency of ICA will decrease continuously.
- **GADA** are detectable with a frequency of 80–90 % in newly manifested T1D, in about 40 % of LADA patients and 5–10 % of gestational diabetes patients. They too decline over the course of the disease but persist longer than ICA.

- **IA2 antibodies** are less frequent than ICA or GADA being demonstrable in 50–70 % and 30–50 % of children/adolescents and adults with newly manifested T1D, respectively.
- **IAA** show the highest sensitivity in children younger than 5 years (90–100 %). In children older than 12 years, IAA are detectable only in about 40 % and in adults in 20–30 %.
- **ZnT8** antibodies are detectable in 60–80 % of T1D patients. They can also be found in patients negative for all other T1D specific autoantibodies. The combined presence of detectable autoantibodies against ZnT8, GAD65, IA2, and insulin increases the likelihood of T1D to about 98 % [6].

Limitations of the assays relate to the general characteristics of assays for the detection of specific antibodies. The specificity may vary depending on the antigens used in the assay. Frequently, quality control is hampered by the absence of well-characterised control samples. Special laboratory equipment, facilities, and training of technicians are required. These issues significantly raise the cost per test, unless the tests are restricted to a few reference laboratories. There is an ongoing search for alternatives that will solve these shortcomings.

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