EUROIMMUN Medizinische Labordiagnostika AG

Type I diabetes mellitus

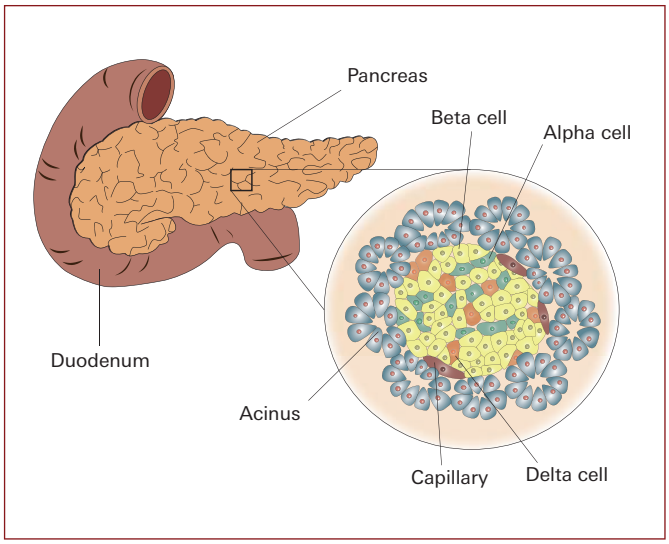
Testing for disease-relevant autoantibodies

- To support the diagnosis of type I diabetes mellitus including LADA
- Important tool for the differentiation from other forms of diabetes such as type II
- Autoantibodies described as predictive and early markers

Course and forms of type I diabetes mellitus

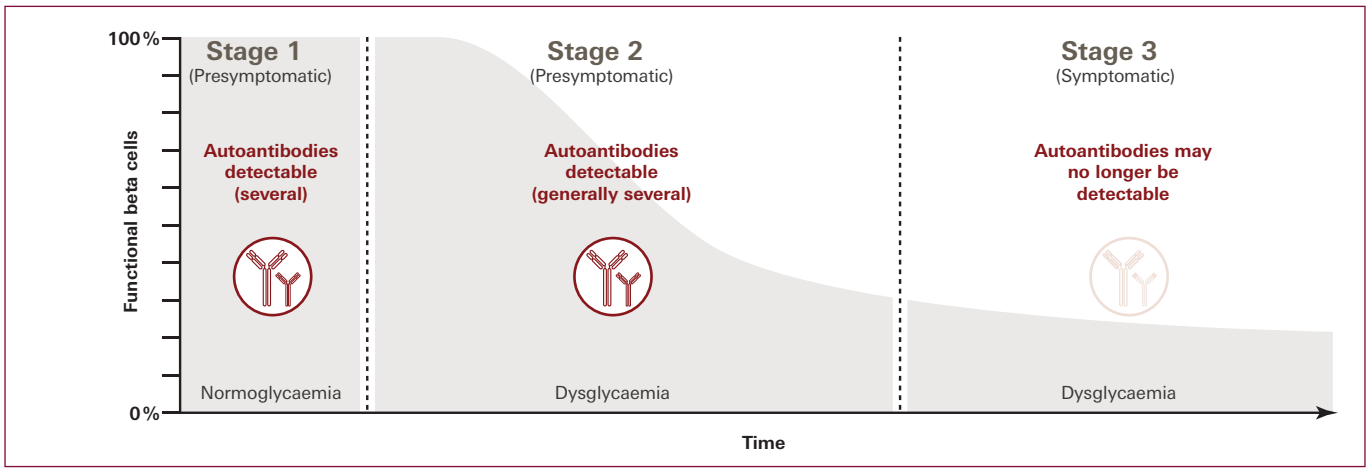
Type I diabetes mellitus (insulin-dependent diabetes mellitus, T1DM) is a chronic autoimmune disease in which the beta cells of the pancreatic islets of Langerhans are selectively destroyed through the mediation of T lymphocytes and specific autoantibodies (AAb) against beta cells. As a result, the pancreas is unable to produce insulin and the blood glucose level can no longer be regulated.

The exact cause is still unclear, but genetic predisposition and infections are considered risk factors. Although the disease often starts in childhood or at the beginning of puberty, it can also occur in adults. The global annual incidence of T1DM is estimated to be about 130,000 new cases in persons under the age of 20,[1] and the incidence in children is currently estimated to be increasing by 3 to 4% per year in countries with a high standard of living.[2] Patients generally require lifelong treatment with exogenous insulin. The earlier T1DM is diagnosed and treated, the better the prognosis.



1 Islet cells of Langerhans with beta cell in the pancreas

A special form of T1DM is LADA (latent autoimmune diabetes in adults). It manifests around the age of 25 and is characterised by a mild course during which insulin dependence slowly develops. LADA is often initially misdiagnosed as type II diabetes mellitus, a non-autoimmune form of diabetes. Therefore, the detection of disease-specific autoantibodies is important to aid in the diagnosis of T1DM and to differentiate the disease from other forms of diabetes.[2–5]

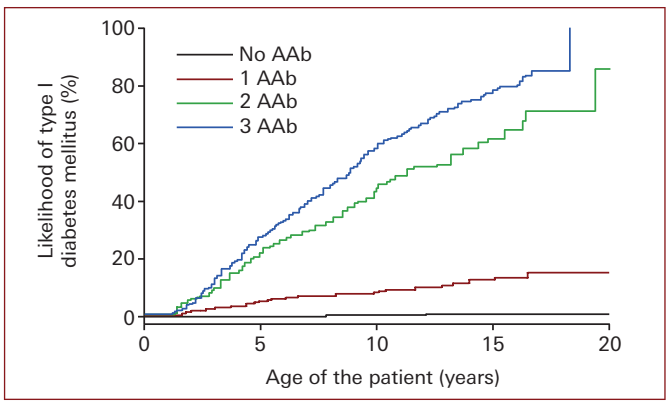


2 Stages of T1DM *(adapted after Insel et al.[6] und ElSayed et al.[4])*

Occurrence of disease-specific autoantibodies

The results of many international studies have shown that several specific autoantibodies directed against various pancreatic islet cell antigens (ICA) are associated with T1DM (▷ p. 3). These often occur several months to years before the disease manifests, which has led to the classification of T1DM into stages. (▷ Fig. 2).[6, 4] The prevalence of each ICA varies greatly with age (often peaking in childhood and declining with increasing age). At least one ICA can be detected in 85–90% of patients with new-onset T1DM at the time of diagnosis.[3]

The number of antibody specificities present correlates with the likelihood of developing T1DM (▷ Fig. 3)[7]. As autoantibodies are important predictive early markers,[3, 4, 8] guidelines describe the antibody screening as useful, for example, in individuals at increased risk of developing the disease to identify presymptomatic T1DM.[4]



3 Increasing likelihood of developing T1DM with increasing number of different specific autoantibodies
(adapted after Ziegler et al.[7])

Autoantibodies associated with type I diabetes mellitus

Anti-glutamic acid decarboxylase antibodies (GADA)

- Directed against glutamic acid decarboxylase (GAD), which catalyses the conversion of glutamic acid to gamma-aminobutyric acid, an inhibitory neurotransmitter that stimulates the production of proinsulin
- Occurrence: often in very high concentrations with long persistence
- Prevalence: 65–80% in newly diagnosed patients[3]
- The most sensitive marker in LADA patients[9]
- GADA also occurs, for example, in stiff-person syndrome, a neurological autoimmune disease associated with muscle stiffness and spasms.[10]

Anti-tyrosine phosphatase antibodies (IA2A)

- Directed against insulinoma-associated antigen 2 (IA2), an enzymatically inactive tyrosine phosphatase that is expressed in beta cells and neuroendocrine tissues and is involved in the regulation of insulin secretion
- Occurrence: often together with other disease-specific autoantibodies
- Prevalence: 65–80% in newly diagnosed patients[3]
- High diagnostic sensitivity in children and adolescents regarding rapid progression to manifest type 1 diabetes mellitus

Anti-zinc transporter 8 antibodies (ZnT8A)

- Directed against zinc transporter 8 (ZnT8), a transmembrane cation transporter that is expressed on the cell membrane of secretory granules in beta cells
- Occurrence: in 26% of patients with type I diabetes mellitus with no detectable autoantibodies against GAD, IA2 or insulin[11]
- Prevalence: 60–80% in patients at the beginning of the disease[11]

Anti-islet cell antibodies (ICA)

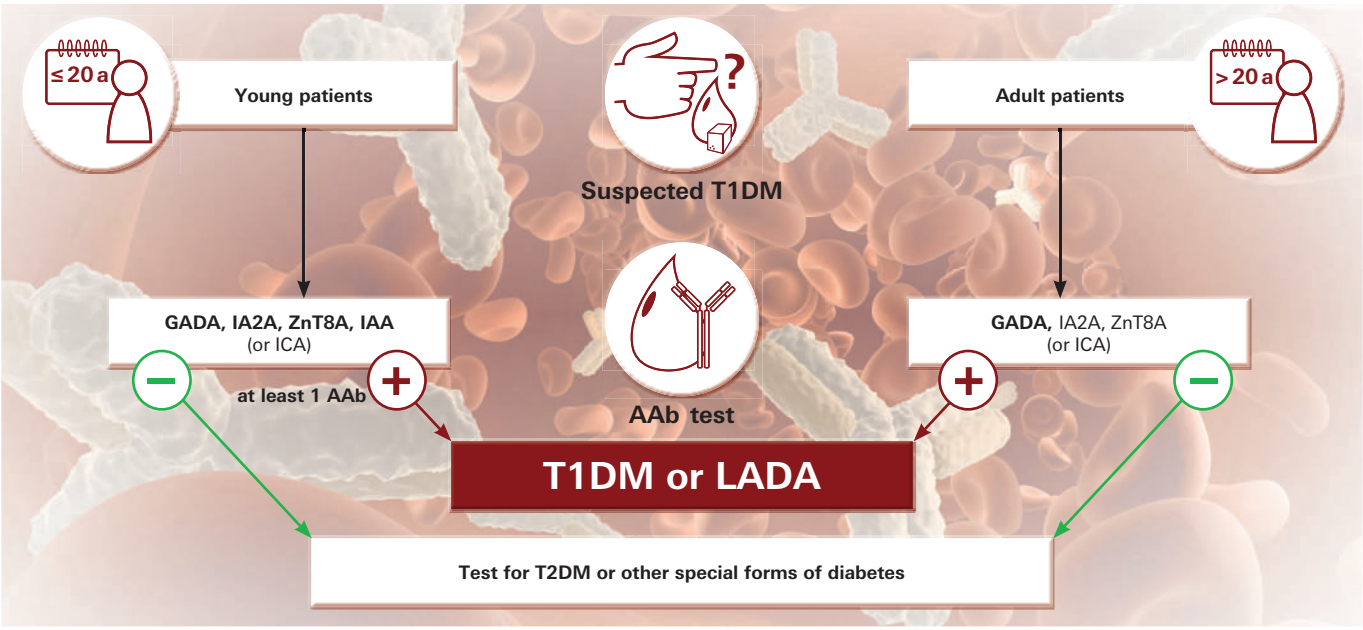
- All antibodies directed against endocrine cells of the pancreas
- Detectable using indirect immunofluorescence test (IIFT)
- Prevalence in manifest T1DM: 80–90%[12]
- Most ICA bind to the antigens GAD, IA2 and/or ZnT8.

Anti-insulin autoantibodies (IAA)

- Occurrence: in the majority of paediatric patients, less frequent with increasing age
- Determination under insulin therapy is not recommended, as IAA induced by exogenous insulin cannot be distinguished from IAA against the body's own insulin.

The prevalence data on this page should be treated with caution due to the heterogeneity of the data between studies.

Possible diagnostic application of diabetes-associated antibodies



4 Example scheme *(adapted after Holt et al.[8], Thaler et al.[13] as well as international guidelines)*: The determination of autoantibodies can be performed in sequences, with confirmation of suspected T1DM with the first positive test. The combined determination of all antibodies is useful up to the age of 20 due to the age-dependent antibody prevalences. From the age of 20, it may be advisable to test for GADA first and then for IA2A or ZnT8A. The combined determination of autoantibodies against all four antigens provides the most reliable detection of T1DM at the onset of the disease (up to over 96% of cases[14]). Direct quantitative determination of autoantibodies is preferable.[8, 13]

EUROIMMUN offers many test systems for the determination of AAb associated with diabetes:

Test system	Test name	Antibodies against	Substrate/antigen	Order no.
ELISA	Anti-GAD ELISA	Glutamic acid decarboxylase (GAD)	Antigen-coated microplate wells	EA 1022-9601 G
	Anti-IA2 ELISA	Tyrosine phosphatase (IA2)		EA 1023-9601 G
	Anti-GAD/IA2 Pool ELISA	Glutamic acid decarboxylase (GAD) Tyrosine phosphatase (IA2)		EA 1022-9601-1 G
	Anti-Zinc Transporter 8 ELISA	Zinc transporter 8 (ZnT8)		EA 1027-9601
IIFT	IIFT Pancreas (Monkey)	Pancreatic islet cells (IC)	Primate pancreas	FA/FC 1020-####

Up to 30% of T1DM patients develop further autoimmune diseases such as autoimmune thyroiditis, autoimmune gastritis and coeliac disease, so further diagnostics are recommended.[15]

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