SMART Medical Review

Immunology and Clinical Approach to Adult-Onset Type 1 Diabetes

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Abstract: Misdiagnosis of type 1 diabetes (T1D) remains a significant clinical concern, often leading to delays in appropriate treatment to prevent its complications. Accurate and timely diagnosis is critical to optimize patient outcomes, yet distinguishing T1D from other forms of diabetes—particularly type 2—can be challenging, especially in adults. This review highlights the importance of precise and accurate diagnostic strategies by focusing on key clinical and biochemical markers, particularly the presence of islet autoantibodies (IAABs) and reduced C-peptide levels, which are indicative of autoimmune β-cell destruction characteristic of T1D. By synthesizing current literature-limited in some areas-, we evaluate diagnostic pathways that leverage these markers to improve diagnostic accuracy. Additionally, we discuss treatment approaches, emphasizing the central role of insulin therapy and the potential use of adjunctive therapies to enhance glycemic control. This review aims to provide clinicians with practical guidance to refine diagnosis and management of T1D, ultimately reducing the burden of misdiagnosis and improving long-term outcomes.

Key words: *Type 1 diabetes, insulin, autoantibodies, diabetic ketoacidosis, autoimmune, endotypes, β-cell, C-peptide.*

Outline:

1. Introduction

Diabetes is classified into type 1 (T1D), type 2 (T2D), specific types of diabetes due to other causes, gestational diabetes. T1D in the past called juvenile-onset diabetes can occur at any age. It is common for patients with adult-onset T1D to be misdiagnosed as having T2D, which can lead to delayed insulin initiation and subsequent complications. Accurate diagnosis requires autoantibody and C-peptide testing. Proper classification is crucial for personalized management and precision medicine.

2. Background

This article aims to provide practical advice on identifying adult-onset autoimmune diabetes and some suggestions on the best treatment.

A summary of the data related to the diagnosis and presentation of T1D in adults include:

- Adults, like children, can experience progressive autoimmune β-cell destruction, necessitating early insulin initiation to avoid hyperglycemia and diabetic ketoacidosis (DKA).[1-3]
- Misdiagnosis of T1D as T2D is reported in up to 40% of adults. The current obesity pandemic contributes to this, making the classic lean T1D phenotype less common.[3]
- The T1D Exchange registry indicates higher DKA rates at diagnosis in children, decreasing with age, and a higher likelihood of overweight/obesity at diagnosis in adults.[3]
- There are some features that should raise suspicion of T1D in adults: younger age at diagnosis

Abbreviations used in this paper: T1D, type 1 diabetes; T2D, type 2 diabetes; DKA, Diabetic Ketoacidosis; IAAB, islet autoantibody; LADA, Latent Autoimmune Diabetes in Adults; BMI, body mass index; ADA, American Diabetes Association; DM, diabetes mellitus; GAD Ab, glutamic acid decarboxylase autoantibodies; IAA, Insulin autoantibodies; IA-2 Ab, tyrosine phosphatases islet antigen 2 autoantibodies; ZnT8 Ab, zinc transporter 8 autoantibodies; ICA, Islet cell autoantibodies; GLP-1, glucagon-like peptide-1.

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(<35 years), lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and high plasma glucose levels (>300 mg/dL) paired by low C-peptide levels or rapid insulin requirement.[4-6]

- Autoantibody testing should generally complete the diagnosis, however there may be limitations particularly in individuals above the age of 35 (see below).[7]
- Adult-onset T1D is common: nearly 40% of U.S. adults with T1D[8] and about 50% in the UK[9] were diagnosed after age 30. After a peak in adolescents, T1D incidence declines between 30 and 40 years of age, to increases again after age 40 with a lower peak later in life.[2,10]
- Among people with T2D, the rate of islet autoantibody (IAAB) positivity (which suggests T1D) ranges from 9.7% in Europe[11] to 5.9% in the US[12], with 6.4% in those overweight or obese.[13]
- Patients with T2D who are positive for islet autoantibodies and not needing immediate insulin are often referred to as having LADA (Latent Autoimmune Diabetes in Adults)[14] but are more appropriately defined as having T1D if autoimmunity is the primary cause of β-cell impairment.[6]

Known mechanistic differences related to age (summarized in Table 1)

- The rate of β-cell destruction is most rapid in young children (<8 years), slower in older children (>12 years), and the slowest in adults.[15]
- In children, islet autoimmunity occurs primarily in the first 6 years of life. It is not clear when the autoimmune process stared in those who developed T1D in adulthood.
- Some adults maintain enough islet cell function to prevent DKA for years but will eventually need insulin as insulin secretion declines.[16]
- Age appears to be a proxy of specific immune and metabolic functions: for example, glutamic acid decarboxylase autoantibodies emerge as a sole marker of autoimmunity and pancreatic cell

Table 1. Differences of autoimmune diabetes presenting in childhood or adulthood

	Children	Young Adults (18-40 years)	Older Adults (>40 years)
% with 1 IAAB	9%	15%	76%
% with multiple IAAB	81%	85%	24%
% with detectable non-fasting C-peptide at 3-5 years after onset*	46%	78%	
Proportion requiring insulin after 6 years	100%	94%	77%
BMI at onset	underweight: 12-16% normal: 63-65% overweight: 9-13% obese: 11-12%	underweight: 7-14% normal: 55-63% overweight: 14-27% obese: 9-12%	underweight: 2-6% normal: 37-52% overweight: 27-50% obese: 10-15%
DKA at onset	40%	24-30%	19%
Proportion with other autoimmune diseases	thyroid disease**: 21-23% celiac disease: 0.9-1.4%	thyroid disease**: 20% celiac disease: 0.8%	thyroid disease**: 17-18% celiac disease: 0.4-0.6%
T1D genetic risk	High T1D genetic risk scores	Less frequent T1D-associated HLA genotypes. Lower T1D genetic risk scores	

IAAB: islet autoantibodies, BMI: body mass index, DKA: Diabetic Ketoacidosis, HLA: Human Leucocyte Antigen. T1D: type 1 diabetes

* ≥0.017 nmol/L

**: either hyperthyroidism or hypothyroidism

Data are from [3,14,15,29,35-37]

infiltrates are different in older versus younger onset T1D.[17,18]

- Younger age is associated with a different regulation of inflammatory responses compared to older age. In young ages, there is predominant IFNγ and TNFα secretion, while IL-10 secretion predominates later in life.[19]
- Other factors like body mass index (BMI), ethnicity, intensity of inflammatory responses, cytokine types, islet phenotypes and pro-insulin processing may be at play, but more data are needed from adult populations.[20]
- This heterogeneity suggests the presence of different "endotypes", whose identification can help guide treatment.[21]

3. Diagnosis

The diagnostic process starts with the suspicion that the person may have autoimmune diabetes rather than T2D.

Who to suspect

The American Diabetes Association (ADA) has proposed criteria to guide the assessment of an individual affected by T1D (see Table 2).

Strategy

The ADA Standards of Care[22] recommend measuring IAABs in every patient where T1D is suspected. The proposed interpretation is as follows and a modified strategy is proposed in Figure 1.

- If IAAB are positive = T1D (no matter which, how many, and how high).
- If IAAB are negative and age <35, no monogenic DM, or C-peptide <0.6 ng/ml (<200 pmol/L) = T1D.
- If IAAB are negative age >35 or age <35 and features of T2D* = undetermined DM. Test C-peptide now and within 3 years. If C-peptide <0.6 ng/ml (<200 pmol/L) = T1D.
- If IAAB are negative, age >35, and C-peptide > 1.8 ng/ml (>600 pmol/L) = T2D.

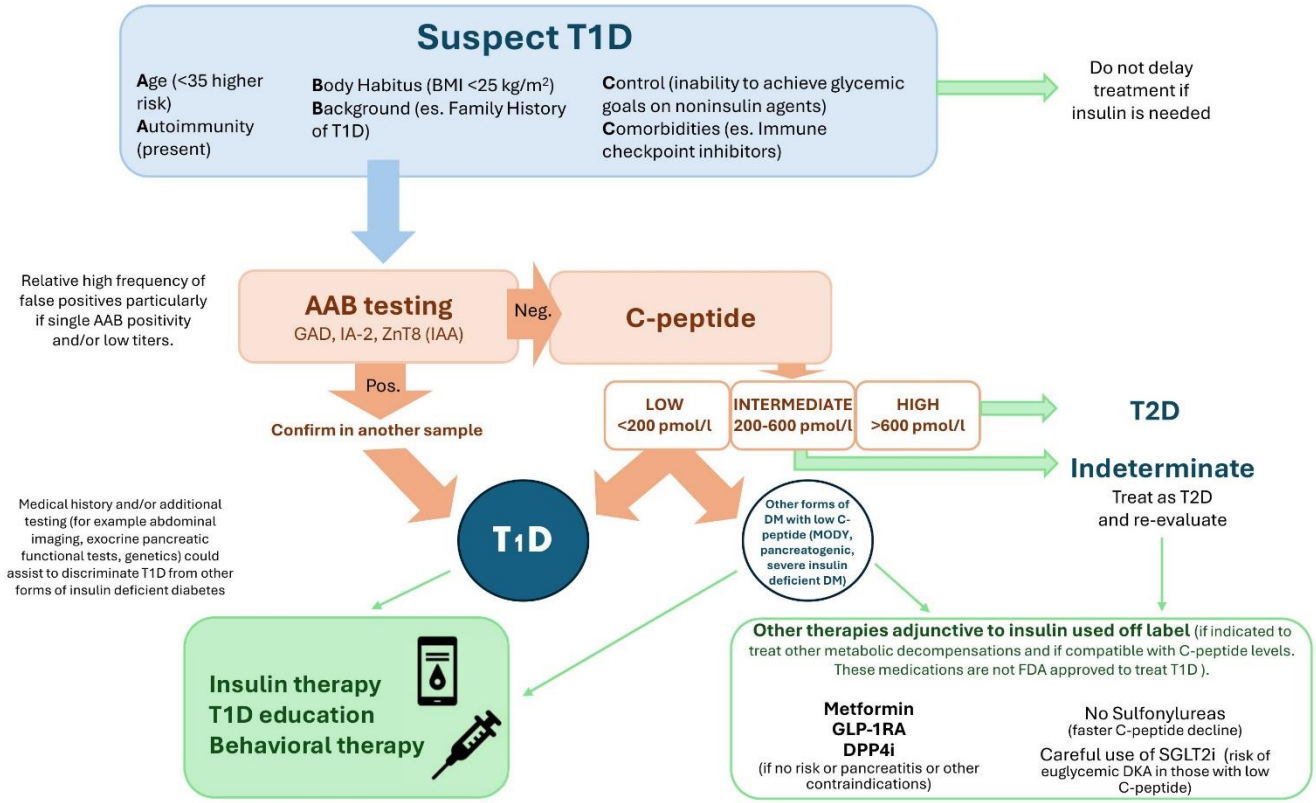
*Features of T2D are: BMI ≥25 kg/m^2, absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia; of less importance: non-White ethnicity, family history of T2D, longer duration and milder severity of symptoms prior to presentation, features of the metabolic syndrome, and absence of a family history of autoimmunity.

Due to the risk of IAAB falsely positive or fluctuating results[23], a confirmatory test is advisable[24], particularly in those with low titers and single autoantibody type (see Figure 1). The diagnosis remains undetermined for patients over 35 or those under 35 with features of T2D, necessitating C-peptide testing and follow-up to complete the diagnosis. This approach, however, delays the diagnosis and insulin should be started if indicated by metabolic deterioration.[25] This approach categorizes as having T1D those with severe insulin-deficient diabetes as defined by Ahlqvist et al.[26] or other forms of insulin-deficient diabetes (for example, pancreatitis-associated). While the treatment will be insulin-based for these forms of diabetes, a proper classification may guide education and therapy, including possible

Table 2. AABBCC approach proposed by the American Diabetes Association (ADA)[22]

Acronym	Category	Example	Notes (not in ADA Standards of Care)
A	Age	Individuals <35 years old	
A	Autoimmunity	Personal or family history of autoimmune disease or polyglandular autoimmune syndromes	People with T1D are prone to other autoimmune disorders
B	Body habitus	BMI <25 kg/m^2	However, studies in adults with autoimmune diabetes showed mean BMIs in the overweight or obese category
B	Background	Family history of T1D	But ~90% of people who develop T1D do not have a known relative with the disease
C	Control	Inability to achieve glycemic goals on noninsulin therapies	Insulin is needed to maintain acceptable metabolic control
C	Comorbidities	Treatment with immune checkpoint inhibitors for cancer can cause acute autoimmune diabetes	

Figure 1.



preventive treatments. No strategies have been proposed to discriminate T1D from other forms of diabetes, but a careful collection of medical history could help (pancreatitis, transplant).

Islet autoantibodies

IAAB indicate an active autoimmune process directed against the pancreatic β-cells; however, they are not pathogenic as the β-cell destruction appears to be mediated by T-cells.

Autoantibody testing should be prompted by the criteria listed in Figure 1 however, the individual criteria overlap among diabetes types and their absence should not exclude the T1D diagnosis. The following are predictors or markers of T1D: autoantibody directed to glutamic acid decarboxylase (GAD Ab), insulin (IAA), tyrosine phosphatases islet antigen 2 (IA-2 Ab), and zinc transporter 8 (ZnT8 Ab). Islet cell autoantibodies (ICA) could also be detected. GAD Ab should always be tested as it is the most frequently detected IAAB in adults. IAA becomes positive within 14 days post-exogenous insulin injection and therefore may not always indicate an active autoimmune response.

How to interpret autoantibody positivity

Multiple IAABs increase the risk of progression to clinically manifest T1D (Stage 3 T1D) in healthy individuals. However, a diagnosis of autoimmune diabetes (with hyperglycemia) can be made with a single IAAB, especially in adults as multiple IAABs are less common.[27] IAAB titers can fluctuate, with 25-30% of single IAABs turning negative at a second confirmatory measure.[12,23] It is recommended to use a standardized method to minimize the variation of test accuracy across laboratories and antigen types. High specificity is crucial to minimize false positives, especially when the disease is rare. The presence of multiple positive autoantibodies reduces the proportion of false positive tests.

In summary, to limit the impact of false positivity:

- Use high-specificity tests performed in laboratories that meet the Islet Autoantibody Standardization Program (IASP) performance standards (more information can be obtained from the IASP coordinating center at the University of Florida).[28]
- Repeat the autoantibody testing on a separate occasion.
- Measure all known IAABs, besides GAD Ab.
- Restrict testing to those with clinical features suggestive of autoimmune diabetes.

People with IAAB-positive diabetes require insulin treatment more often than IAAB-negative subjects.[14,26] Proper diagnosis excluding false IAAB positivity is crucial to avoid overtreatment of individuals with T2D.

C-peptide levels

Measuring fasting or stimulated C-peptide levels is a validated method to determine insulin production and assist distinguishing between T1D and T2D as shown in Figure 1. Concomitant serum glucose levels should be checked to interpret C-peptide results as C-peptide levels can be falsely low under certain conditions, such as hypoglycemia (blood glucose <3.9 mmol/L or <70 mg/dL) or in severe hyperglycemia/DKA.[24] Since C-peptide levels vary at the time of T1D clinical diagnosis depending on a faster or slower insulin secretion decline, C-peptide alone is insufficient for discriminating T1D from T2D or other diabetes types (Figure 1).

Can genetic testing help?

Genetic risk scores for T1D have been utilized to identify individuals at risk for future disease onset. However, the discriminatory ability of these studies may differ in populations of diverse ancestries, necessitating further research. In children, neutral or protective HLA-DR/DQ genotypes were more frequent in the oldest age group (13-17 years).[18]

Studies done in non-immediately insulin requiring autoimmune diabetes in adults (defined as LADA) confirmed that it is genetically close to childhood onset T1D, but the genetic load of T1D risk alleles is less than childhood-onset T1D, particularly at the major histocompatibility complex region.[29]

Overall, however, genetic testing knowledge is insufficient to inform treatment selection.

4. How to treat it

Understanding differences in disease pathogenesis at different ages (endotypes) will guide the treatment selection. In patients with features of both T1D and T2D, treatment for both conditions could be considered for example to address the peripheral insulin resistance or the need for weight loss. Treatment should be as follows:

Insulin:

- It is the primary treatment
- It is initiated immediately in cases with severe metabolic decompensation at presentation (primarily younger adults with marked hyperglycemia and acidosis) or after the failure of non-insulin agents in the presence of IAABs, when the diagnosis of T1D is confirmed.
- In pre-symptomatic T1D, sequential HbA1c monitoring indicates disease progression and the need for insulin treatment. In metabolically asymptomatic IAAB-positive children, an HbA1c increase of 10% indicates disease progression with a median of 1 year. In children, however, the progression is faster and different cut-offs should be established for adults.
- Early intensive insulin treatment provides protection against complications (DCCT/EDIC studies[30,31]) and likely contributes to glycemic control.[32]

Other Drugs:

- **Metformin**: Increases insulin sensitivity and reduces weight, but no direct benefits on glycemic control in T1D.
- **DPP-4 Inhibitors**: Inhibit the enzyme dipeptidyl peptidase-4 (DPP-4) which degrades incretin hormones like glucagon-like peptide-1 (GLP-1) increasing insulin secretion, suppressing glucagon secretion and slowing gastric emptying. May improve glycemic control and preserve β-cell function; no safety concerns reported.
- **GLP-1 Receptor Agonists**: Effective in reducing HbA1c in T2D by enhancing insulin secretion, suppressing glucagon secretion, slowing gastric emptying and reducing appetite; promising results in preserving β-cell function in young adults recently diagnosed with T1D with further randomized clinical trials needed.[33]
- **Thiazolidinediones**: Activate the peroxisome proliferator-activated receptor gamma (PPARγ) increasing insulin sensitivity by redistributing fat, reducing inflammation and circulating free fatty acids. Limited studies with conflicting data.
- **Sulfonylureas**: Increase insulin secretion by causing β-cell membrane depolarization. Not indicated due to rapid decline of C-peptide levels.
- **SGLT-1/2 Inhibitors**: Inhibit glucose reabsorption in the renal tubules and reduce blood glucose levels; ensure sufficient C-peptide/insulin reserve to avoid the known risk of euglycemic ketoacidosis.

Even if used adjunctive to insulin in patients with T1D, the above listed drugs are not FDA approved for T1D treatment.

5. Other considerations

The frequency of DKA among adults at T1D diagnosis is lower than that for children have higher C-peptide levels at clinical diagnosis and experience a slower decline in β-cell function over time. However, incorrect assumptions lead to misdiagnosis of T1D in adults, delaying needed insulin treatment. Approaches able to modify the natural history of T1D are under investigation, and the first drug able to delay T1D onset in children and young adults – Teplizumab - was approved by the FDA in 2022. It was shown that Teplizumab can help preserve beta cell function in children, adolescents and young adults newly diagnosed with T1D.[34] It was not investigated if teplizumab or other disease-modifying therapies could be beneficial for adult-onset T1D with residual C-peptide secretion.

6. Conclusions

It is important to remember that autoimmune diabetes can be diagnosed at any age. A significant proportion of cases are diagnosed in adults, but the specific mechanisms involved in the loss of insulin secretion in the context of autoimmunity at different ages are not fully understood.

Though these patients will need insulin therapy, other treatments that target concomitant underlying causes of hyperglycemia (for example insulin resistance) could also be helpful to optimize metabolic compensation and preserve β-cell function. Further research is crucial to selecting appropriate therapies (adjunct to insulin) for autoimmune diabetes patients.

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Dr. Anna Casu conceptualized the article and wrote the manuscript. Ananya Bhatheja performed literature searches and contributed to manuscript writing. Dr. Tina K. Thethi contributed to manuscript writing.

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