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Review

Adult-onset type 1 diabetes: early detection, differential diagnosis, and emerging disease-modifying therapies

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ABSTRACT

Adult-onset type 1 diabetes (T1D) likely exceeds childhood-onset in absolute numbers, yet many cases are underestimated due to misclassification as type 2 diabetes. This pragmatic review synthesizes current evidence on epidemiology, pathophysiology, diagnosis, and early disease-modifying therapy in adults. Incidence data from 32 countries indicate that adults account for a median 42% of new T1D diagnoses. Autoimmunity follows the pediatric, HLA-restricted paradigm, but β-cell dysfunction appears slower, reflected by measurable C-peptide for years. Misdiagnosis delays insulin initiation, increases ketoacidosis risk, and forfeits opportunities for β-cell–sparing interventions. We present a four-step diagnostic algorithm integrating an islet autoantibody panel with a fasting or random C-peptide–to-glucose ratio, and highlight red-flag scenarios warranting repeat testing. We also propose a hypothetical, risk-enriched four-step pathway to identify presymptomatic T1D in adults that begins with a higher HbA1c trigger, uses enrichment to raise pretest probability, and reserves full autoantibody testing for high-probability individuals. Given low prevalence and false-positive risk, this pathway needs prospective validation before routine care. We review adult and adolescent evidence for targeted immunomodulators, including teplizumab, abatacept, rituximab, low-dose anti-thymocyte globulin, ustekinumab, golimumab, baricitinib and alefacept, as well as β-cell–directed agents such as verapamil and imatinib, and discuss emerging HLA- and autoantibody-defined endotypes that may predict response. Collectively, current evidence supports routine autoimmune diabetes screening in adults with new-onset diabetes.

Abbreviations: **ADA**, American Diabetes Association; **ATG**, Anti-thymocyte Globulin; **AUC**, Area Under the Curve; **BMI**, Body Mass Index; **CGM**, Continuous Glucose Monitoring; **CGR**, C-peptide-to-glucose ratio; **CTLA-4**, Cytotoxic T-Lymphocyte Antigen-4; **DKA**, Diabetic Ketoacidosis; **DR3**, HLA-DR3; **DR4**, HLA-DR4; **GADA**, Glutamic Acid Decarboxylase Autoantibody; **GLP-1**, Glucagon-like Peptide-1; **GST**, Glucagon stimulation test; **HbA1c**, Glycated hemoglobin; **HLA**, Human Leukocyte Antigen; **HOMA2-B**, Homeostatic Model Assessment of β-cell Function; **IA-2A**, Insulinoma-Associated Protein-2 Autoantibody; **IAA**, Insulin Autoantibody; **ICI**, Immune Checkpoint Inhibitor; **IL-2**, Interleukin-2; **IL-21**, Interleukin-21; **IV**, Intravenous; **JDRF**, Juvenile Diabetes Research Foundation; **LADA**, Latent Autoimmune Diabetes in Adults; **MACE**, Major Adverse Cardiovascular Events; **PD-1**, Programmed Cell Death Protein 1; **PI:C**, Proinsulin-to-C-Peptide Ratio; SGLT2i, Sodium–Glucose Cotransporter-2 inhibitor; **T1D**, Type 1 Diabetes; **T1D-GRS2**, Type 1 Diabetes Genetic Risk Score 2; **T2D**, Type 2 Diabetes; **TFH**, T follicular helper cell; **TXNIP**, Thioredoxin-interacting protein; **ZnT8A**, Zinc Transporter 8 Autoantibody.

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1. Introduction

Type 1 diabetes (T1D) has traditionally been regarded as a disease diagnosed primarily in childhood or adolescence. However, recent epidemiologic data clearly demonstrates a significant increase in the diagnosis of T1D in adults, challenging historical perceptions and underscoring the need for awareness and early detection in all age groups [1]. Globally, population-based registries continue to document an approximate 2–3 % annual increase in childhood T1D incidence [2], and mounting evidence indicates that a substantial majority of new cases present in adulthood ($\geq$ 18 years) [3]. A recent multi-national registry analysis covering eight high-income jurisdictions reported that, among young adults aged 15–39 years, the incidence of T1D increased by approximately 0.5–6.0 % per year between 2000 and 2020 [4]. A 2022 systematic review that collated incidence data from 32 countries reached the same conclusion, reporting that adults aged $\geq$ 20 years contribute a sizeable, although highly variable, fraction of incident T1D across all regions examined [5]. During the COVID-19 pandemic, several national and international registries reported a higher frequency of diabetic ketoacidosis (DKA) at diagnosis and signals of increased incidence of new-onset T1D, particularly in children and adolescents, although the magnitude and persistence of these changes varied between countries and study designs [6–8]. Causality remains uncertain and findings are likely confounded by changes in health-care access, care-seeking behaviour, testing patterns and diagnostic coding during the pandemic, so current data are best interpreted as indicating a modifier of presentation patterns rather than a clearly established driver of long-term T1D epidemiology.

Several mechanisms have been proposed to explain a potential increase in adult-onset T1D cases. Genetic predisposition, particularly linked to specific human leukocyte antigen (HLA) class II alleles, remains fundamental, but not sufficient for T1D. Cohort and family studies show that an additional environmental trigger is required, with enteroviral infection, shifts in gut microbiota, and diet-related changes in intestinal permeability among the leading candidates [9,10]. Genome-wide work in more than 1 300 autoantibody-positive adults confirms that the same nine susceptibility loci identified in childhood disease (HLA, PTPN22, INS, IL-2RA, CTLA4 and others) drive risk in later life, yet the high-risk DR3-DR4 genotype is less frequent, while moderate-risk combinations (for example DR3/X or DR4/X) are more common [11] This broader and generally lower genetic load seems to be associated with slower loss of β-cell function supporting the view that clinically overt disease in adults often requires a stronger or more prolonged environmental or metabolic trigger. Recognition of this epidemiologic situation is clinically critical, as adult presentations of T1D are often different than in childhood, leading to misclassification as type 2 diabetes (T2D) and dangerous delays in insulin initiation. In addition, accumulating evidence indicates that T1D is not a single homogeneous entity, but comprises different immunologic and metabolic “endotypes” that differ by age at presentation, autoantibody profile, genetic risk load, and rate of β-cell loss [12]. Appreciating this heterogeneity sharpens the diagnostic distinction from T2D and opens the door to tailored interventions in adult practice.

A polygenic risk-based analysis in the UK Biobank has not only shown evidence of an almost constant, age-independent incidence of T1D until the age of 60 but also reported a median body-mass index (BMI) of 27 kg/m^2 in those late-onset cases [13]. This mirrors the upward shift in BMI seen across the general population and underlines that excess weight no longer excludes autoimmune diabetes. Historically, adult-onset diabetes was almost invariably presumed to be T2D, driven by insulin resistance, metabolic syndrome, and obesity [14]. This assumption often led clinicians to overlook autoimmune etiologies in adults, particularly in those with a less fulminant course or typical T2D-phenotypes such as overweight or older age at onset [15,16]. This underscores the challenge of distinguishing T1D from T2D in adults and highlights that viewing T1D as a purely pediatric disease may delay proper recognition and treatment. Contemporary studies further demonstrate that a substantial proportion of adult patients with new-onset diabetes actually have an autoimmune form of diabetes, often presenting initially with moderate hyperglycemia and a slower progression compared with pediatric–onset cases [17]. Misclassification of T1D cases as T2D carries significant clinical risks. Delayed initiation of insulin therapy due to presumed T2D leads to suboptimal glycemic control, a higher incidence of DKA, especially in those receiving treatment with sodium-glucose-type 2-transporter inhibitor (SGLT2i) when prescribed for individuals with unrecognised autoimmune insulin deficiency [18,19]. Early and accurate classification is therefore essential for optimal patient management and prognosis.

This practical review aims to help clinicians identify adult–onset autoimmune diabetes promptly, reduce misclassification, initiate appropriate insulin early, and open the door to emerging disease–modifying therapies.

2. Pathophysiology and clinical presentation

2.1. Pathophysiology of autoimmunity in type 1 diabetes

T1D results from autoimmune–mediated destruction of insulin–producing pancreatic β-cells [20]. Although the precise triggers remain incompletely defined, the disease arises at the intersection of genetic susceptibility, environmental factors, and immune dysregulation. Genetic risk is conferred predominantly by HLA class II alleles, most notably HLA–DR3 and DR4, which together account for a large fraction of inherited predisposition to T1D [21,22]. Beyond HLA, more than 60 additional risk loci, including *PTPN22, INS, IL2RA, CTLA4, IFIH1, TYK2, CLEC16A* and *UBASH3A*, have been implicated in T1D [23,24]. Individually, these variants exert modest effects, but in aggregate they shape overall genetic susceptibility and underpin genetic risk scores/polygenic risk scores that improve discrimination of autoimmune from non–autoimmune diabetes, including adults with ambiguous clinical features [25,26]. Across the age spectrum, earlier–onset T1D carries higher genetic risk (including HLA enrichment), whereas adult–onset shows a lower average T1D genetic burden [27]. However, even this extended genetic architecture does not determine onset. Environmental “hits” such as viral infections (e.g., enteroviruses), early–life diet patterns, and gut microbiome alterations are assumed to provoke or accelerate islet autoimmunity [28].

Autoimmunity in T1D involves both humoral and cellular immune components (Fig. 1). Cytotoxic T lymphocytes, mainly autoreactive $CD8^+$ T cells, are the principal effectors that infiltrate pancreatic islets and directly eliminate β-cells [29,30]. Islet autoantibodies arise in parallel and serve as biomarkers of the autoimmune process rather than its main drivers. Diabetes related autoantibodies, particularly against insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A) can appear months to years before clinical hyperglycemia, serving as early markers of β–cell–directed autoimmunity [29,31]. Regulatory T cells, whose task is to maintain peripheral tolerance, are quantitatively or functionally impaired in T1D, permitting unchecked effector activity against β-cells [32]. Additional contributors, including $CD4^+$ T-helper cells, pro-inflammatory cytokines, and B cells, interact with the cytotoxic T-cell response and amplify β-cell destruction [30].

2.2. Clinical differences between adults and children in type 1 diabetes

The phenotype of T1D in adults mostly differs from that seen in children. In children, T1D usually presents abruptly with severe hyperglycemia or DKA, whereas adults more often show a gradual onset that can resemble T2D at first presentation [33,34]. Progression risk must be interpreted by stage. In the TrialNet Pathway to Prevention cohort, 5–year progression to clinical T1D was lower in adults than children for single autoantibody positivity (8.2 % vs 22 %) and stage 1

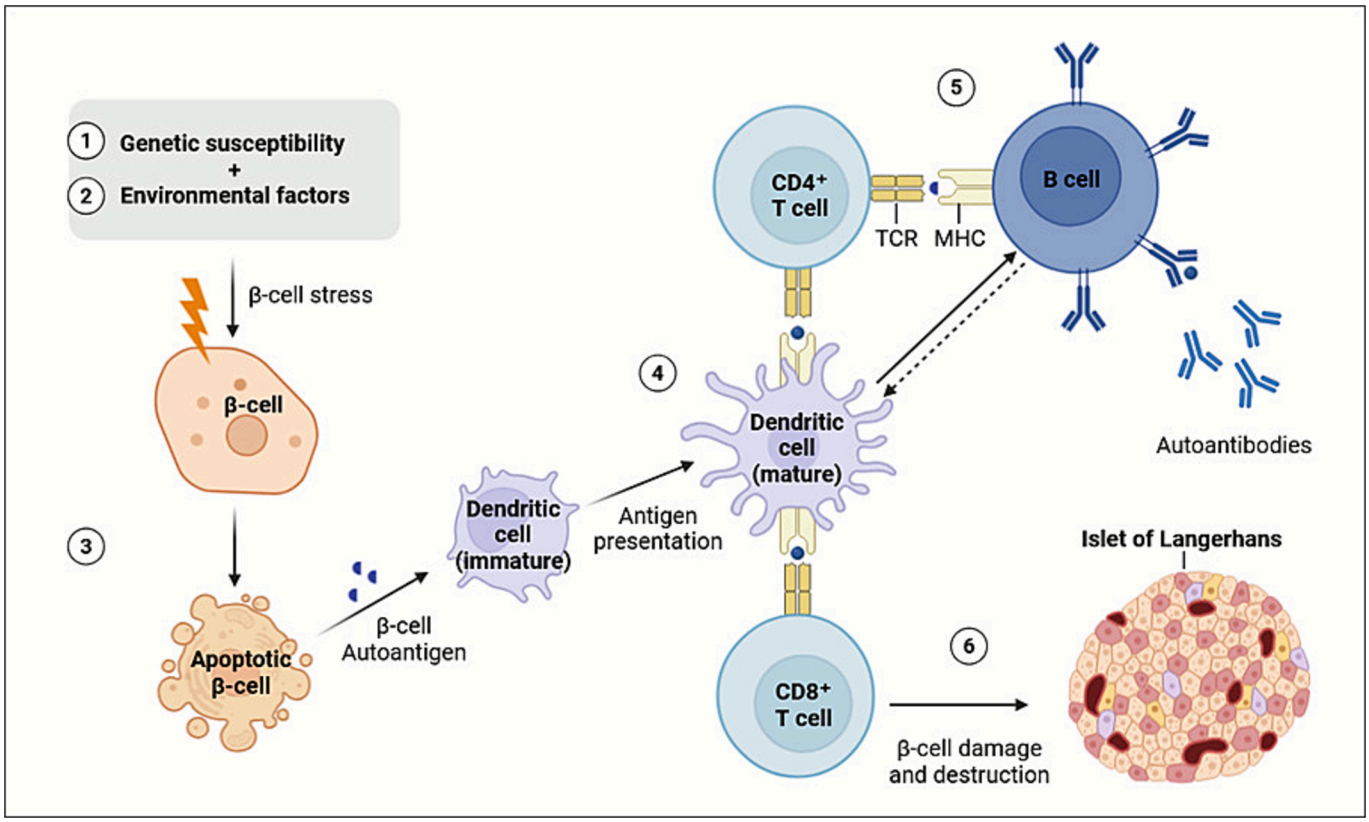

Fig. 1. Pathophysiology in adult-onset autoimmune diabetes. (1) Genetic susceptibility weakens central deletion of islet-reactive T cells and impairs peripheral regulatory-T-cell control. (2) Environmental factors—viral infection, microbiota shifts or metabolic stress—activate innate immune cells in the gut or pancreas. (3) Within pancreatic tissue, additional stressors (remodelling, virus, ER stress) and macrophage-derived IL-1β/TNF initiate β-cell apoptosis, releasing β-cell antigens. (4) Dendritic cells capture these antigens and migrate to the pancreatic lymph node. (5) There they present β-cell peptides to naïve $CD4^+$ and $CD8^+$ T cells, driving cytotoxic differentiation and helping B-cell autoantibody production. (6) Autoantibody-producing B cells, including $CD20^+$ B cells that act as non-professional antigen-presenting cells, and activated T cells enter islets of Langerhans, forming insulitic infiltrates. $CD8^+$ cytotoxic T cells kill β-cells through perforin–-granzyme release, FAS–FASL signalling and pro-inflammatory cytokines. Paediatric insulitis often shows denser $CD20^+$ B-cell infiltrates than adult lesions, consistent with age-linked immunopathology.

(multiple autoantibodies with normoglycemia; 17 % vs 47 %), whereas adults and children with stage 2 had comparable 5–year risks (~78 % in both groups) [35]. Similar age-related patterns have been observed in first-degree relative cohorts, where multiple- or double–islet-autoantibody positivity in children and adolescents carries the highest medium- and long-term progression risk, while autoantibody-positive adults tend to progress more slowly [36,37]. Adults may present with features usually associated with T2D, such as higher BMI, dyslipidemia, or hypertension, which complicates diagnosis. In this setting of individuals with clinical features of T2D, isolated low-titer GAD antibody positivity has limited positive-predictive value. Assay methodology influences risk prediction. Electrochemiluminescence (ECL) formats, especially ECL-GADA, preferentially detect high-affinity, disease-relevant antibodies and improve clinical correlation and predictive value compared with standard radiobinding, which is particularly useful when isolated low-titer RBA-GADA is found in adults [38,39]. Historically, the term latent-autoimmune diabetes of adults (LADA) has been used to define GAD positive persons with a clinical T2D phenotype [17,40].

As insulin deficiency develops early, adults with T1D experience two- to three-fold higher rates of severe hypoglycaemia than insulin-treated T2D counterparts, a gap driven by obligatory exogenous insulin, dysregulation of glucagon release and a progressive blunting of sympathoadrenal responses [41]. Early biochemical confirmation with a full islet-autoantibody panel plus if necessary fasting or random C-peptide (or a C-peptide-to-glucose ratio) can secure the diagnosis and prevents therapeutic delay [42,43]. Longitudinal C-peptide data underscore a strong age effect on β-cell decline: At diagnosis most children younger than seven years have C-peptide concentrations below 0.20 nmol/L, whereas more than 60 % of adults maintain values above this threshold even five years after diagnosis [44,45]. Persisting C-peptide, even at low concentration, is associated with smoother glucose profiles, fewer severe hypoglycemic episodes and a lower incidence of microvascular complications [45]. Large immunogenetic cohort studies, investigations that relate genetic risk loci (chiefly HLA haplotypes) to longitudinal immune markers such as autoantibody profiles and C-peptide trajectories, show that age-related differences reflect distinct endotypes in which adaptive autoimmunity progresses at different speeds; the slower adult trajectories create a wider therapeutic window for β-cell preservation [8,17,33,34].

One more adult-specific T1D-aspect to be considered is the immune checkpoint inhibitor (ICI) induced diabetes. In large contemporary cohorts, it occurs in approximately 0.5 % of ICI-treated adults, with reported rates ranging from 0.1 % to 1.4 % across different studies [46–49]. The risk is higher with PD-1/PD-L1 plus CTLA-4 combination therapy than with PD-1 monotherapy. Most cases arise within the first year of treatment (median onset approximately six months), although later events can occur, which argues for extended vigilance [48,49]. This drug induced T1D presents typically with a sudden onset, severe hyperglycemia/hyperglycemic hyperosmolar status, DKA, and may show T1D-specific antibodies in a substantial subset of cases. ICI-T1D can be predicted by the presence of certain antibodies and HLA alleles. Specifically, anti-GAD antibodies and certain HLA-DR4 alleles are associated with an increased risk of developing ICI-T1D [48,49]. As with classic T1D, insulin substitution therapy must be started immediately,

however, identifying new-onset diabetes as insulin-deficient diabetes in this special population of elderly people with cancer is challenging and requires awareness and a screening/monitoring strategy for this new, potentially life-threatening adverse event. Early case reports of ICI-induced diabetes also described radiological or biochemical evidence of pancreatitis in some patients, suggesting that checkpoint blockade can affect both the endocrine and exocrine pancreas [50].

3. Diagnosis and differentiation from type 2 diabetes

Accurate differentiation of adult-onset T1D from T2D is pivotal, because the two entities diverge markedly in therapeutic needs and prognosis. When progressive β-cell failure in autoimmune T1D is mistaken for insulin-resistant T2D, oral agents fail to control glycemia and the probability of DKA rises steeply [51]. By contrast, timely recognition of autoimmunity permits earlier insulin replacement, which corrects the physiological deficit. This eventually lowers DKA risk at presentation, and helps preserve endogenous C-peptide, which is linked to fewer severe hypoglycemic events and microvascular complications [44,45].

The following chapter outlines a concise, evidence-based diagnostic pathway:

Clinical evaluation – phenotypic cues that raise the pre-test probability of insulin-deficient diabetes.
Laboratory testing – islet-autoantibodies and if necessary, a fasting or random C-peptide-to-glucose ratio that objectively confirm or refute autoimmunity.
Structured decision-making – a four-step algorithm specifying immediate management when results are unequivocal and a follow-up plan for grey-zone cases

Implementing this stepwise approach minimizes diagnostic delay, reduces acute metabolic decompensation, and ensures that adults with autoimmune diabetes receive appropriate therapy before further irreversible β-cell loss occurs.

3.1. Clinical evaluation

Clinical evaluation remains the cornerstone of diabetes diagnosis. Classic DKA–alerting symptoms, such as abdominal pain, nausea, vomiting, Kussmaul breathing or fruity breath odor, should be queried first, as ketoacidosis is both common and life–threatening at adult–onset T1D [51]. Polyuria, polydipsia, fatigue, blurred vision and unexplained weight loss are also frequent but less specific [21].

Even a seemingly indolent presentation should trigger suspicion: poor glycemic control on oral agents, sudden deterioration in glucose profiles, mild-to-moderate ketosis or an unexpectedly high propensity for hypoglycemia soon after insulin initiation all favor an autoimmune etiology. A personal or family history of organ-specific autoimmunity (Hashimoto thyroiditis, vitiligo, pernicious anemia, coeliac disease or Addison's disease) further elevates pre-test probability [52]. Previous transient hyperglycemic episodes and first–degree relatives with autoimmune diabetes should also prompt laboratory testing [33]. An additional adult-specific scenario is new-onset hyperglycemia in late pregnancy. Hyperglycemia first detected in the second or third trimester is usually classified as gestational diabetes (GDM), but in a subset of women this presentation reflects evolving autoimmune T1D rather than classical GDM [53]. In women with GDM who are positive for at least one diabetes-related autoantibody and who display features such as a rapid need for insulin therapy and/or ketonuria, clinicians should strongly consider an autoimmune etiology and arrange islet autoantibody testing and close postpartum follow-up [53].

During follow-up, several treatment-response patterns should prompt an immediate re-evaluation of an original T2D diagnosis:

- Rapid secondary failure of dual oral therapy
- Unexpected hypoglycemia on modest basal-insulin doses
- Euglycemic or ketotic DKA precipitated by a SGLT-2i

These red flags indicate underlying insulin-deficient diabetes. Any of these findings merits immediate antibody and C-peptide reassessment.

3.2. Laboratory testing

A clear biochemical pathway is essential once adult–onset diabetes raises suspicion of autoimmunity. The first priority is safety, and clinicians should promptly assess the risk of DKA. In individuals with symptoms or signs suggestive of DKA, such as vomiting, tachypnoea, abdominal pain or marked hyperglycaemia, a venous or capillary blood gas and/or urinary ketone dipstick measurement should be obtained. Even modest hyperglycemia may be associated with DKA, and a pH $<$ 7.30 or bicarbonate $<$ 18 mmol/L mandates immediate insulin and fluid resuscitation [51].

With acute danger excluded, the next task is to determine etiology. The ADA Standards of Care 2025 endorse a tiered antibody strategy: start with GADA; if the result is negative or equivocal, add IA-2A and/or ZnT8A [54]. When feasible, measuring a complete panel of the four major islet autoantibodies (GADA, IA-2A, ZnT8A and IAA) in a single blood draw can shorten the diagnostic pathway. However, given the low pre-test probability of T1D in many unselected adults, a tiered strategy (GADA first, followed by IA-2A and/or ZnT8A only when needed) remains a pragmatic and cost-efficient default in routine care. We therefore recommend at least GADA plus one additional antibody in all adults in whom autoimmune diabetes is suspected, and a full panel in those with a high pre-test probability. IAA is often the first autoantibody to appear in young children at risk for T1D but is less frequently positive in adults. Once a patient has been on exogenous insulin for approximately 10–14 days, IAA measurement becomes difficult to interpret, because the injected insulin itself acts as an antigen and elicits de novo insulin-binding antibodies. In that setting, a positive IAA result is more likely to reflect treatment-induced immunization than pre-existing autoimmunity. For that reason, we reserve IAA testing for insulin-naïve adults when samples can be obtained before the first insulin dose.

- High-positivity pattern: The presence of two or more distinct islet-autoantibody specificities is consistently associated with a high positive-predictive value for progression to insulin dependence in adults. A single high-titer GADA alone is less specific in adults and should be interpreted with additional antibodies or C-peptide [54].
- Low-positivity pattern: A solitary low-titer GADA ($\leq \approx$ 200 IU/mL, assay-dependent) appears in up to 10 % of phenotype-concordant type 2 cases and confirms T1D in only about two-thirds of adults, leaving a false-positive rate near 30 % [55,56]. When classification depends on such a low-titer result:
  - o add IA-2A or ZnT8A, either of which markedly improves specificity [57,58]
  - o order IAA only if the patient is insulin-naïve and the sample can be drawn before therapy.
- Genetic adjunct: A genetic score such as T1D-GRS2 (AUC 0.88 for distinguishing T1D from T2D) may offer a tie-breaker when antibody data remain inconclusive [25].

This sequence (GADA first, IA-2A and ZnT8A as secondary tests, IAA reserved for insulin-naïve adults) aligns the diagnostic workflow with current ADA guidance while minimizing unnecessary assays in routine practice.

Assessment of endogenous insulin secretion follows once autoantibody tests are inconclusive. Before sampling, ensure that plasma glucose is between 70 and 250 mg/dL (4.0–13.9 mmol/L), the individual has fasted or at least three hours have passed since the last meal and any rapid-acting insulin dose, ketoacidosis or a hyperosmolar state is absent,

and a wash-out period of one week after high-dose corticosteroids and two weeks after starting a glucagon-like peptide-1 (GLP-1) receptor agonist or an SGLT2i has elapsed. Draw blood into a standard serum or lithium-heparin tube and separate the serum or plasma within two hours to minimize peptide degradation [54]. Within those pre-analytic boundaries, the ADA propose two practical fasting (or random) C-peptide cut-offs: $\leq$ 0.20 nmol/L indicates marked β-cell failure, whereas $\geq$ 0.60 nmol/L is more typical of pronounced insulin resistance and makes autoimmune diabetes unlikely [54]. Intermediate values become more informative when related to the concomitant glucose concentration. The fasting C-peptide-to-glucose ratio (CGR) is calculated as C-peptide in pmol/L divided by plasma glucose in mg/dL. In a cohort of 3 751 adults, Fritsche and colleagues showed that a CGR < 2 pmol/mg/dL (0.008 nmol/mmol) corresponds to a Homeostatic Model Assessment of β-cell function (HOMA2-B) of about 50 and is therefore suggestive of insulin-deficient diabetes [43]. When venipuncture is impractical, a spot urine C-peptide-to-creatinine ratio below 0.20 nmol/mmol offers a needle-free surrogate with comparable diagnostic value [59].

Intact proinsulin and, in particular, the proinsulin-to-C-peptide ratio (PI:C) may be considered as exploratory adjuncts when insulin or HOMA indices and C-peptide are discordant [60]. A disproportionately elevated proinsulin or high PI:C indicates endoplasmic reticulum (ER) stress and impaired prohormone processing, a pattern repeatedly observed in insulin-resistant states and linked to poorer β-cell function and higher future T2D risk [61,62], whereas uniformly low insulin, C-peptide, and proinsulin are more consistent with primary insulin deficiency [63,64]. As a practical caveat, insulin immunoassays differ by platform and some show cross-reactivity with proinsulin, which can artifactually raise "insulin" and mislead HOMA estimates; knowing the local assay characteristics (and, when needed, measuring intact proinsulin or PI:C) can help resolving such discrepancies. These adjunct tests are not part of standard diagnostic algorithms yet.

3.3. *Structured diagnostic decision-making*

An integrative diagnostic approach (Fig. 2) that combines clinical findings with laboratory data is essential for distinguishing T1D from T2D. The four steps outlined below follow the framework set out in the 2025 ADA Standards of Care [54].

- **Step 1 – Suspicion filter and safety triage**
  - Diagnose first, test second. In adults with newly detected hyperglycemia, autoantibody assays should be ordered only when clinical features raise genuine suspicion of autoimmune diabetes. The ADA summarizes those features with the mnemonic AABBCC:
    - **A**ge: T1D can present at any age; diagnosis in early adulthood (for example < 35 years) raises suspicion for autoimmune diabetes, but older age does not exclude it. Treat age as a probabilistic cue, not a hard cut-off
    - **A**utoimmunity: Personal or family history of an organ-specific autoimmune disorder (e.g., thyroiditis, vitiligo, coeliac, Addison)
    - **B**ody habitus: Lean or non-centrally obese build (often BMI < 25 kg/m^2) increases the prior probability of autoimmune diabetes, but overweight and obesity are common in contemporary T1D and do not exclude autoimmunity; insulin resistance and excess adiposity may even unmask an underlying autoimmune process (accelerator hypothesis) [65].
    - **B**ackground: First-degree relative with T1D
    - **C**ontrol**:** Inability to meet glycemic targets on non-insulin therapy, or ketoacidosis at presentation
    - **C**omorbidities: Conditions that provoke autoimmune β-cell damage (e.g., immune-checkpoint-inhibitor treatment, cystic fibrosis, chronic pancreatitis)
  - Count the cues:
    - Any one of these cues justifies moving to Step 2 (autoantibodies ± C-peptide).
    - If none apply and the phenotype is typical for T2D, manage initially as type 2 but continue to reassess if glycemic control deteriorates.
  - Safety check:
    - If diabetic ketoacidosis is suspected, obtain a venous or capillary blood gas; if pH < 7.30 or HCO_3^- < 18 mmol/L → Evaluate hospital admission/start fluid resuscitation/stop physical exercise/and start insulin.
- **Step 2 – Staged laboratory work–up**
  - 2a. Islet-autoantibodies
    - Measure at least GADA plus one additional antibody (IA-2A, ZnT8A or, in insulin-naïve adults, IAA).
    - Diagnostic rule-in:
      - Any two antibodies, irrespective of titer, confirm autoimmune diabetes.
    - Single low-titer result:
      - If no second antibody is found, label the case indeterminate and proceed to C-peptide assessment; repeat the full panel only if clinical suspicion rises or metabolic control worsens.
  - 2b. β-cell reserve
    - If the antibody panel is negative but clinical suspicion of autoimmune diabetes persists, assess β-cell reserve with C-peptide and a paired glucose.
    - Preferred Approach:
      - Use a stimulated C-peptide whenever feasible, ideally in the form of a standardized mixed-meal tolerance test (MMTT) with repeated measurements over 2–4 h in research settings. In routine practice, a simplified approach using a usual mixed meal or carbohydrate-rich snack (e.g. a typical breakfast with at least moderate carbohydrate content) with a single blood sample 1–2 h later is often sufficient. For follow-up, sampling should, as far as possible, be performed at a similar postprandial time point after a comparable meal to allow meaningful comparison over time
    - Pragmatic alternative in routine practice:
      - If only "spot" laboratory testing is possible, a random C-peptide can still be informative, even more if concomitant glucose and timing relative to the last meal and insulin dose are documented. Values obtained very shortly after a large prandial insulin bolus or in the fasting state should be interpreted with particular caution, as exogenous insulin suppresses endogenous secretion.
    - Interpretation:
      - C-peptide < 0.20 nmol/L → profound insulin deficiency → T1D
      - C-peptide > 0.6–0.8 nmol/L → secretion preserved → supports T2D or another non-autoimmune etiology
      - Values in between warrant a repeat using the same sampling protocol in 6–12 months (or sooner if control deteriorates)
    - Optional adjuncts:
      - A fasting C-peptide-to-glucose ratio (CGR) can refine grey-zone results (e.g., CGR < 0.008 nmol/mmol suggests insulin deficiency)
- **Step 3 – Act on clear evidence**
  - If Autoimmunity confirmed (high-titer or ≥ 2 antibodies) **or** CGR below threshold
  - → start insulin therapy (by default basis-bolus therapy combining basal insulin with prandial rapid acting insulin) and provide structured education
  - Consider referral for disease-modifying trial screening if available
- **Step 4 – Resolve the grey zone**
  - Stage 2 T1D – presymptomatic autoimmunity with dysglycemia:
    - Six-month metabolic re-check: in individuals with confirmed islet autoimmunity who do not yet meet diagnostic criteria for

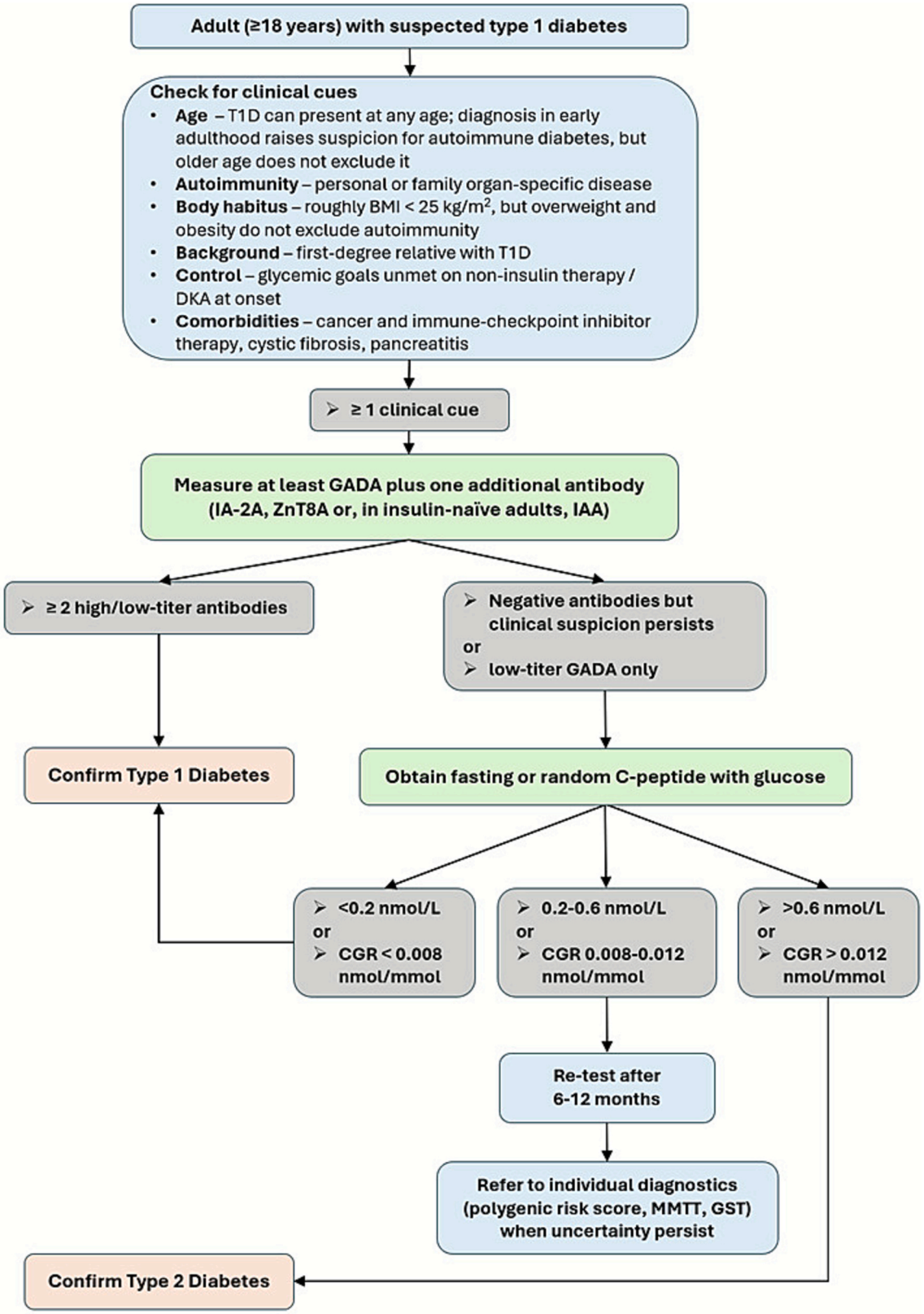

Fig. 2. Flowchart for investigating of suspected type 1 diabetes in newly diagnosed adults. Modified according to (54). Abbreviations: BMI, Body-Mass Index; T1D, Type 1 Diabetes; DKA, Diabetic Ketoacidosis; CGR, C-peptide-to-Glucose Ratio; MMTT, Mixed-Meal Tolerance Test, GST, Glucagon Stimulation Test; GADA, Glutamic Acid Decarboxylase Autoantibody; IA-2A, Islet Antigen-2 Autoantibody; ZnT8A, Zinc Transporter 8 Autoantibody; IAA, Insulin Autoantibody.

diabetes (stage 2 T1D), repeat a standardized stimulated C-peptide (preferably using the same protocol as at baseline) together with HbA1c after 6–12 months to monitor β-cell decline and progression towards stage 3.

- o Stage 3 T1D – established diabetes with uncertain etiology:
  - ■ In adults who already fulfil diagnostic criteria for diabetes but have an equivocal phenotype (possible stage 3 T1D vs T2D), a stimulated C-peptide and antibody review can be repeated under standardized conditions to clarify classification and guide insulin intensification.
  - ■ Endocrinology referral if doubt remains: consider a glucagon-stimulated C-peptide in a standardized laboratory setting, blinded CGM review (e.g. time above range $>$ 10 % of readings above 140 mg/dL [7.8 mmol/L] over 10–14 days), and where available, research-grade T1D genetic-risk scores (not yet recommended for routine practice).
- o Progression triggers (reclassify to stage 3 T1D and/or intensify insulin):
  - ■ Stimulated C-peptide $<$ 0.20 nmol/L, or
  - ■ $\geq$ 30 % fall in stimulated C-peptide within 12 months, together with biochemical criteria for diabetes, should prompt classification as stage 3 T1D and timely initiation or intensification of insulin therapy.

4. Therapeutic perspectives

Historically, therapy for T1D was conceived almost exclusively as insulin replacement. Contemporary evidence shows that preserving even small amounts of residual endogenous insulin—reflected by detectable C-peptide—attenuates glycemic excursions, improves time-in-range, approximately halves the incidence of severe hypoglycemia, and reduces long-term microvascular risk [45,66–68]. Because immune-mediated β-cell destruction unfolds over months to years, interventions initiated while C-peptide remains detectable may alter this trajectory. Accordingly, the therapeutic focus is beginning to broaden beyond hormone substitution to include disease-modifying approaches that seek to slow immune-mediated β-cell loss, where feasible.

The agents summarized below (Table 1.) represent the first generation of disease-modifying strategies with adult clinical data. They fall into two broad classes:

- Targeted immunomodulators aimed at dampening or re-educating the autoimmune response (e.g., anti-CD3, CTLA-4-Ig, B-cell depletion).
- β-cell stress mitigators and functional supporters that help surviving β cells withstand metabolic and inflammatory pressure (e.g., verapamil, imatinib) and may synergize with immunotherapy.

Table 1

Disease–modifying therapies evaluated in adults with type 1 diabetes. Abbreviations: AUC – Area under the curve; ATG – Anti-thymocyte globulin; CD20 – Cluster-of-differentiation 20 surface antigen; CTLA-4-Ig – Cytotoxic T-lymphocyte–associated protein-4 immunoglobulin fusion protein; ER-stress – Endoplasmic-reticulum stress; G-CSF – Granulocyte colony-stimulating factor; GLP-1 RA – Glucagon-like peptide-1 receptor agonist; IL-21 – Interleukin-21; IL-12/23 – Interleukin-12/23; TNF-α – Tumor necrosis factor alpha; JAK – Janus kinase; LFA-3 – Lymphocyte function-associated antigen-3; IV – Intravenous; mAb – Monoclonal antibody; SC – Subcutaneous; TFH – T-follicular-helper cell; TXNIP – Thioredoxin-interacting protein.

Therapy	Mechanism of action	Intervention	Population & stage	Results
Teplizumab (69–72)	Anti-CD3 mAb; induces partial T-cell exhaustion and regulatory $CD8^+$ cells	Single 12–14-day IV course (in recent trials: two 12-day courses 6 months apart)	Stage 2 at-risk relatives; new-onset stage 3 T1D (mainly children/ adolescents)	In stage 2, delays clinical T1D by ≈2 years; in stage 3, consistently preserves stimulated C-peptide for $\geq$ 1–2 years with modest effects on insulin dose and HbA1c
Ustekinumab (78)	Anti-IL-12/23 p40 mAb; reduces Th1/Th17-mediated inflammation	Weight-based s.c. dosing at weeks 0 and 4, then every 12 weeks for ≈1 year	Adolescents with new-onset stage 3 T1D	Phase 2 trial: well tolerated and preserves stimulated C-peptide vs placebo with modest glycaemic benefit
Golimumab (79)	Anti-TNF-α mAb; blocks pro-inflammatory cytokine signalling	S.c. injections every 2 weeks for 52 weeks	Children and young adults with new-onset stage 3 T1D	Phase 2 trial: higher stimulated C-peptide AUC at 1 year vs placebo with lower insulin requirements and some improvement in glycaemic control
Baricitinib (80)	Oral JAK1/JAK2 inhibitor; blocks multiple cytokine pathways	4 mg orally once daily for 48 weeks	Adolescents and adults with new-onset stage 3 T1D	Phase 2 trial (BANDIT): met primary endpoint; ~minimal decline in stimulated C-peptide vs substantial decline with placebo, with lower insulin dose and improved CGM metrics
Alefacept (81, 82)	LFA-3–Ig fusion protein; selectively depletes memory T cells ($CD2^+$)	Two 12-week courses of 15 mg i.m. weekly, separated by 12 weeks off-treatment	Adolescents and young adults with new-onset stage 3 T1D	Phase 2 T1DAL study: sustained preservation of stimulated C-peptide at 12–24 months vs placebo with reduced insulin dose and fewer major hypoglycaemic events
Abatacept (73, 74)	CTLA–4–Ig – blocks CD28 co–stimulation, reduces T–cell activation	10 mg/kg IV day 1, 14, 28 then every 4 weeks for 24 months	New–onset (<100 days since diagnosis, 6–45 years)	Stimulated C-peptide release significantly higher after 2 years
Rituximab (75, 76)	Anti–CD20 – depletes B cells that present β–cell antigen	Four weekly IV infusions 375 mg m^{-2}	New–onset (<3 months since diagnosis, 8–40 years)	Stimulated C-peptide release significantly higher, significantly lower HbA1c values and lower insulin requirement after one year, effects not maintained after 2 years
Low–dose ATG ± G–CSF (77, 87, 88)	Polyclonal T–cell depletion (spares T–regs); G–CSF promotes tolerance	2-day IV total 4.5 mg/kg with or without s.c. G-CSF; recent MELD-ATG trials with 0.5–2.5 mg/kg ATG alone	New-onset stage 3 T1D (children, adolescents and adults)	Preserves stimulated C-peptide and improves HbA1c vs placebo; MELD-ATG shows efficacy down to 0.5 mg/kg without clear added benefit of G-CSF
Anti–IL–21 + Liraglutide (89)	IL–21 blockade dampens TFH/ autoreactive B cells; GLP–1 RA gives metabolic rest	30 mg SC anti–IL–21 weekly + liraglutide 1.8 mg SC daily for 54 weeks	New–onset (<20 weeks since diagnosis, 18–45 years)	Stimulated C-peptide release significantly higher after 54 weeks, but only when both active ingredients are combined
Verapamil (83, 84)	L-type Ca^{2+}-channel blocker; reduces TXNIP, ER-stress and β-cell apoptosis	120–360 mg orally once daily for 12 months	Adults with new-onset stage 3 T1D; paediatric data from separate trials	Small adult trial showed higher stimulated C-peptide, lower insulin dose and fewer hypoglycaemic events; a larger multicentre phase 2 trial (Ver-A-T1D) is ongoing; first conference reports suggest trends towards β-cell preservation, but full peer-reviewed results are awaited
Imatinib (85)	c–Abl inhibition → reduced ER–stress & innate activation	400 mg orally daily for 26 weeks	New–onset (<100 days since diagnosis, 18–45 years)	Higher C–peptide at 12 months; no difference at 24 months

Teplizumab [69–72] is currently the only approved immunotherapy in T1D, and its indication is to delay progression from stage 2 to stage 3 T1D in adults and children aged ≥ 8 years. Beyond teplizumab, several targeted immunomodulators listed in Table 1, including abatacept [73,74], rituximab [75,76], low-dose anti-thymocyte globulin [77–79], ustekinumab [80], golimumab [81], baricitinib [82], anti-IL-21 + liraglutide [83] and alefacept [84,85], have each demonstrated statistically significant but typically modest preservation of C-peptide in phase 2 trials predominantly in children and adolescents, with variable durability. Among β-cell–directed agents, verapamil [86,87] and imatinib [88] have shown signals of improved C-peptide in early trials, although long-term benefit has not yet been firmly established, particularly in adults. All of these approaches remain investigational, and none is currently approved as a disease-modifying therapy for stage 3 T1D.

Combination regimens that integrate agents affecting cellular stress responses (e.g. verapamil) with immune modulation are conceptually attractive, but current evidence is limited to early-phase trials, and the optimal combinations, sequences, and treatment durations remain unknown. Adults may be particularly suitable candidates for such combination strategies, because adult-onset T1D often shows a slower decline in C-peptide and a longer period of residual insulin secretion than childhood-onset disease, potentially widening the window in which immuno-metabolic combinations have time to act. At the same time, adults are highly heterogeneous with respect to genetic risk, autoantibody profile and insulin resistance, so it remains uncertain which adult subgroups will benefit most. Prospective, staged adult trials are therefore needed before specific combinations can be recommended for routine care.

The emerging pipeline supports a new clinical strategy: detect adults while endogenous insulin secretion is still present, match them to an appropriate immuno-metabolic intervention, and monitor with the same stage specific metrics that guided diagnosis. Data from earlier immunosuppressive trials (e.g. cyclosporin [89]) and from more recent agents such as teplizumab suggest that earlier intervention, closer to diagnosis or even at stage 2, is associated with greater preservation of β-cell function. Most new-onset studies to date have enrolled individuals up to approximately 35–45 years of age, so the potential benefits of such therapies in those diagnosed at older ages remain uncertain. Taken together, these data reinforce the clinical urgency of distinguishing T1D from T2D as early as possible in adults and, where appropriate, initiating disease-modifying therapy while meaningful C-peptide reserve is still present.

5. Is There a Rationale for screening Programs to detect Pre-Type 1 diabetes (Pre-T1D) in Adults?

Disease-modifying agents such as teplizumab [69–71], low-dose anti-thymocyte globulin [77], abatacept [73,74], and verapamil [86,87] have shown that β-cell preservation is possible while endogenous insulin secretion is still present. It is therefore plausible that the benefit will be even greater if treatment begins before overt hyperglycemia, when β-cell mass is higher and metabolic stress lower. This question matters because about 40 % of new cases of autoimmune diabetes are now diagnosed after the age of 30 [90], and long-term cohort data indicate that many adults remain in presymptomatic stages for years before progression to clinical disease. Individuals diagnosed with T1D in adulthood, including those diagnosed at or after age 40, have higher risks of major adverse cardiovascular events (MACE) and all-cause mortality and, on average, poorer glycemic control than population controls, underscoring the clinical relevance of identifying high-risk adults early [91].

A recent study from TrialNet Pathway to Prevention study including 135.914 children (aged < 18 years) and 99.795 adult relatives of individuals with T1D screened showed that progression to stage 3 disease was lower in adults with single autoantibody positivity or stage 1 T1D than in children (5-year risks: single autoantibody, adults 8.2 % vs. children 22 %, $p < 0.001$; stage 1, adults 17 % vs. children 47 %, $p < 0.001$) [35]. However, intriguingly, adults with stage 2 T1D at initial staging oral glucose tolerance test had comparable 5-year progression risks to children (78 % for both groups). A higher proportion of adults progressing to clinical diabetes were single autoantibody positive (40 % vs. 15 %; $p < 0.0001$) [35]. European first-degree relative data show a concordant pattern: in relatives with islet autoimmunity, multiple autoantibodies together with younger age at autoimmunity detection confer the highest 5–20-year progression risks, whereas adults with single autoantibodies progress more slowly but still have a meaningful lifetime risk, which has informed European screening initiatives such as the INNODIA Family & Friends early-stage T1D detection programme [37,92]. The longer adult trajectory widens the therapeutic window but at the same time lowers the positive predictive value of any single screening marker.

General population screening for stage 1 diabetes in adults therefore appears challenging and is unlikely to be justified at present, due to low positive predictive value. Thus, a more targeted screening strategy is needed. Prediabetes is common, whereas true presymptomatic T1D is rare. In a recent adult screening study from the Colorado ASK program of 1087 adults without known diabetes only 0.55 % carried two or more islet autoantibodies, and 3.9 % being positive for just one [93]. With that given prevalence, even a test with 99 % specificity would yield roughly two false positives for every true positive. Marker overlap further complicates matters, as HbA1c, C-peptide, and isolated low-titer GADA frequently mirror pre-T2D. Furthermore, the ensuing psychological and economic burden, such as anxiety, stigma, potential insurance or career limitations, and repeated follow-up visits, cannot be ignored. However, a hypothetical, risk-enriched, stepwise pathway to detect stage 2 T1D could provide a proportionate alternative and would parallel the diagnostic logic already applied to manifest diabetes.

Hypothetical algorithm to identify stage-2 T1D in adults:

(1) Entry trigger. Significant dysglycemia or prediabetes detected during routine HbA1c testing in primary care; a higher cut-off (for example the upper tertile of the 5.7–6.5 % range, ≈ 6.2 %) could serve as the initial filter.

(2) Clinical enrichment. Proceed only if at least one cue is present that raises pre-test probability of islet autoimmunity, such as a lean or centrally non-obese phenotype, pre-existing organ-specific autoimmunity (for example autoimmune thyroid disease, coeliac disease, pernicious anaemia or Addison's disease), a family history of T1D or other autoimmune endocrinopathies, or conditions that predispose to autoimmunity such as trisomy 21 or Turner syndrome.

(3) Antibody confirmation. In the enriched subset, obtain a complete panel (GADA, IA-2A, ZnT8A, and IAA if insulin-naïve). Adults with two antibodies constitute the high-risk group; weaker or negative patterns are considered lower risk.

(4) Risk refinement and follow-up. Adults with two antibodies could then undergo genetic and metabolic refinement (for example a type 1 diabetes genetic risk score and fasting or random C-peptide with concomitant glucose) and might enter prospective metabolic monitoring at defined intervals. Those with weaker or negative antibody results might return to routine care with annual HbA1c so that any subsequent rise in glycemia could re-trigger step (1).

Because adult data on the natural history and psychosocial impact of stage-1 and stage-2 screening remain sparse, such pathway should first be evaluated in a study to clarify predictive value, feasibility, and net benefit. Until such evidence is available, early detection of presymptomatic adult T1D should remain a research endeavor. A composite marker set, combining HbA1c, a multi-antibody profile, and a genetic risk score, may ultimately provide the specificity required for broader implementation, offering a pragmatic bridge between today's therapeutic options and tomorrow's preventive practice while containing the psychological and economic costs of false positives.

6. Conclusion and future directions

Adult-onset autoimmune diabetes has emerged as a common, often overlooked, heterogeneous entity that demands a rethinking of diagnostic reflexes, therapeutic timing and research priorities. Population-based incidence curves from five continents now show that ≥ 35 %, and in some regions > 50 %, of all new T1D diagnoses occur after the age of 20 [1,2,5,94]. These "late" presentations are not merely childhood cases discovered belatedly. Immunogenetic studies suggest distinct endotypes in which adaptive autoimmunity progresses more slowly, frequently preserving clinically useful C-peptide for years [12,21,44,45]. Such biology brings both opportunity and risk. Opportunity, because the longer window before complete β-cell loss could widen access to disease-modifying therapy. Risk, because the indolent metabolic course mimics T2D, resulting in diagnostic delay and postponed insulin initiation [18,95].

Diagnostic imperatives. Misclassification of adult-onset autoimmune diabetes as T2D is a leading, but not the only, preventable contributor to DKA at presentation and to delays in appropriate therapy. A structured laboratory pathway, first-line GADA plus at least one additional antibody (IA-2A, ZnT8A and, in insulin-naïve adults, IAA) followed by a fasting or random C-peptide paired with glucose, helps distinguish severe insulin deficiency from preserved insulin secretion in most adults at the first encounter, while flagging a minority of intermediate cases for follow-up [42,43,96]. Any two antibodies rules in autoimmune diabetes; conversely, a solitary low-titer GADA is equivocal because up to one-third of phenotype-concordant T2D cases show the same finding [17,96]. In that setting, adding IA-2A or ZnT8A markedly increases specificity, whereas repeating the whole panel adds little in adults. If antibody results remain negative or indeterminate, a C-peptide < 0.20 nmol/L, or a fasting C-peptide-to-glucose ratio < 0.008 nmol/mmol, confirms severe insulin deficiency and justifies definitive insulin therapy. Intermediate values should be re-checked at six to twelve months; falling C-peptide, even in the continued absence of antibodies, signals evolving T1D. The integration of continuous ketone monitoring into a structured screening strategy might be a useful to identify T1D in those at high risk. Broad implementation of this antibody + C-peptide algorithm would avert much of the ketoacidosis and microvascular burden that follow diagnostic inertia [18,95]. Extending the lens upstream. Emerging studies suggest that a similar, risk-enriched approach may prove useful even before diabetes is established. Whether presymptomatic screening could one day justify routine clinical use remains uncertain. Robust data on cost-effectiveness, assay harmonization and psychosocial consequences are lacking. Nonetheless, piloting a carefully controlled, evidence-generating screening algorithm now would lay the groundwork for integrating immune-modifying therapies if and when they gain adult approval and consensus support.

6.1. *Therapeutic horizon: from replacement to modification*

The approval of teplizumab marks a shift from insulin replacement to genuine disease modification in T1D. Early immune or metabolic intervention, illustrated by agents such as teplizumab [70], abatacept [73], rituximab [75,76], and verapamil [87,97], can slow β-cell decline, especially when therapy starts while C-peptide remains above approximately 0.20 nmol/L. Efficacy tends to cluster in HLA- or antibody-defined responders and wanes once immunologic activity rebounds, which has led to the hypothesis that rational combination regimens joining β-cell stress–reducing agents (e.g. verapamil) with immune modulation might be required for durable remission. At present, however, combination strategies remain in early-phase development, and the best combinations, sequences and timing are unknown.

Future directions. The confluence of precise, early diagnostics and mechanism-based therapy could provide a realistic opportunity for transforming adult-onset T1D. Within the next decade, routine antibody/CGR screening in every newly diagnosed adult with suspected T1D, **followed by early** immune or metabolic intervention, could shift the disease from inexorable β-cell failure to a manageable, potentially remitting condition. Whether and how combination immunotherapy will contribute to this vision remains to be defined by ongoing and future trials. Realizing this vision will require harmonized laboratory cut-offs, automated decision-support in electronic records, reimbursement for both diagnostic panels and biologics, and cross-specialty networks that funnel eligible individuals into adaptive platform trials. If such an infrastructure is built, the next generation of adults diagnosed with autoimmune diabetes may spend more of their lives in partial remission than in complete insulin dependence.

Data availability statement

No new data were created or analyzed in this study.

CRediT authorship contribution statement

Robert Wagner: Writing – review & editing, Conceptualization. **Martin Füchtenbusch:** Writing – review & editing, Conceptualization. **Michael Hummel:** Writing – review & editing, Conceptualization. **Martin Miszon:** Writing – original draft, Conceptualization. **Andreas Pfützner:** Writing – review & editing, Conceptualization. **Susanne Reger-Tan:** . **Tobias Wiesner:** Writing – review & editing, Conceptualization.

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