SUMMARY (clinical) 4/18/25 ciT1zen science
Type 1 diabetes presenting in adults: Trends, diagnostic challenges and unique features.

ciT1zen science summary

Source: Excerpts from "Type 1 diabetes presenting in adults: Trends, diagnostic challenges and unique features" by Carmella Evans-Molina MD and Richard A. Oram MD, published in *Diabetes, Obesity and Metabolism*, Early View, April 15, 2025.

Summary: The key themes and important findings from a review article focusing on type 1 diabetes (T1D) that presents in adulthood. The article highlights the significant prevalence of adult-onset T1D, the challenges in its diagnosis due to overlap with type 2 diabetes (T2D), and the unique genetic, immunologic, and metabolic features that differentiate it from childhood-onset T1D. The authors emphasize the critical need for expanded research, improved diagnostic tools, and refined classification criteria to address the current under-recognition and misdiagnosis of this condition, ultimately aiming for earlier and more appropriate treatment.

Main Themes and Important Ideas/Facts:
1. Epidemiology of Adult-Onset T1D:

- Adult-onset T1D accounts for a substantial proportion of T1D cases worldwide, with some data suggesting it is more prevalent than childhood-onset T1D due to the longer duration of adulthood.
- While childhood T1D incidence rates may be higher annually, the total number of adult-onset cases over a longer period can exceed childhood cases. For example, in a US study, "the total number of adult-onset T1D cases in the 14-year period (2001–2015) was higher in adults than children (19 174 adult-onset cases versus 13 302 childhood-onset cases)."
- Epidemiological patterns in adult-onset T1D largely mirror childhood-onset disease (e.g., higher incidence in men, Nordic populations).
- There is no clear pattern of elevated risk with increasing age within the adult population, and significant knowledge gaps exist, particularly in low- and middle-income countries.
- The distinction between adult-onset T1D and Latent Autoimmune Diabetes in Adults (LADA) remains controversial, and this sub-classification may hinder accurate diagnosis and treatment. The authors treat adult-onset T1D as a singular entity in this review.

2. Diagnostic Challenges and the Need for Accurate Identification:

- Accurate identification of adult-onset T1D is crucial because it typically necessitates insulin therapy, and misdiagnosis as T2D leads to poor glycemic control and increased risk of complications.

- "The erroneous treatment of those with adult-onset T1D with therapeutics normally used to treat type 2 diabetes (T2D), including dietary modification or oral agents, leads to poor glycaemic control and a higher risk of acute and chronic complications."
- The higher prevalence of T2D in adults (90-95% of adult diabetes cases) lowers the prior odds of T1D, making diagnosis challenging. Features suggestive of T1D in children (low BMI, ketoacidosis, autoantibodies) may be indicative of "atypical" T2D in adults due to these prior odds.
- Misclassification rates are high, with self-reported misdiagnosis occurring in nearly 38% of adults with T1D. Registry and EHR data also show significant misclassification (30-40%).
- Conversely, misclassification of T2D as T1D also occurs, affecting the understanding of adult T1D features.
- The reliance on EHR data for research necessitates careful validation of T1D diagnoses using robust biomarkers.

3. Genetic and Immunologic Features of Adult-Onset T1D:

- While adult-onset T1D shares genetic overlap with childhood-onset disease (HLA and non-HLA loci), adult cases tend to have lower genetic risk scores (GRS), less high-risk HLA heterozygosity, and more protective genotypes.
- "Despite this similarity, a universal observation is that genetic risk for T1D seems to slightly reduce with age, whether measured as individual risk allele frequencies, frequency of high-risk HLA, or when combined into a polygenic score as a T1D GRS."
- Autoantibody associations are similar (GAD65, IA2, ZnT8, insulin, islet cell), but adults more often present with GAD65 positivity and are more likely to be single autoantibody positive at diagnosis.
- High GAD65 levels are associated with rapid C-peptide decline and poorer metabolic control, suggesting prognostic value.
- Adults are more likely than children to revert from multiple to single or no autoantibody positivity.
- Age-related differences may exist in normal ranges for some autoantibodies (e.g., ZnT8). Caution is needed due to the potential for "biologic" false positives in autoantibody testing.
- Pancreas tissue analysis shows age-related differences in insulitis, with "hyperimmune" lesions more common in early childhood-onset T1D. Residual insulin-containing islets are more prevalent in later-onset disease.
- Circulating immune signatures in adult-onset T1D and their age-related changes require further study. T1D may be associated with accelerated immune aging.

4. Metabolic Features of Adult-Onset T1D:

- The applicability of the pre-clinical T1D staging paradigm (based largely on childhood studies) to adults needs further validation. Progression from autoantibody positivity to clinical T1D appears slower in adults.

- "Cross-sectional cohorts like the TrialNet Pathway to Prevention study have shown that progression from either single or multiple autoantibody positivity to clinical T1D diagnosis is slower in adults compared to children."
- Longitudinal C-peptide loss and glycemic patterns in adults before clinical diagnosis are poorly understood due to a lack of natural history data prior to seroconversion.
- Studies comparing beta-cell function decline in adults and children have yielded conflicting results, possibly due to variations in methodology, cohort demographics, and C-peptide assays.
- Some studies suggest a faster decline in children, particularly younger children, while others find no significant age-related differences in the rate of decline.
- "Thus, in aggregate, there remains considerable uncertainty on the extent to which age impacts the rate of β cell loss either before or after clinical diagnosis of T1D."
- At clinical diagnosis, adults may have higher C-peptide levels and are less likely to present with ketoacidosis. They may also experience a longer "honeymoon" period and more frequent clinical remission. Older age of onset is often associated with better glycemic control.
- Obesity and metabolic syndrome are increasingly common in adults with T1D, potentially influencing disease progression, treatment response, and complication development. GLP-1 agonists and SGLT2 inhibitors are being explored as adjuvant therapies in adult T1D.
- Exocrine pancreas loss is a feature of T1D across all ages, but whether age-related differences exist in the extent of this loss is unknown.

5. Approaches for Classification: Practical and Aspirational:

- A high level of clinical vigilance is necessary to avoid misdiagnosis, considering age, other autoimmunity, BMI, family history, glycemic control, and comorbidities (AABBCC mnemonic).
- Data-driven diagnostic tools integrating clinical features and biomarkers (autoantibodies, GRS) are under development. Age at diagnosis <40 years, BMI <25 kg/m^2, and insulin initiation within 3 years are strong predictors of T1D in adults.
- Recent consensus guidelines from the EASD and ADA provide a staged approach to diagnosing adult-onset T1D, emphasizing autoantibody testing as the first step. However, these guidelines have limitations, including a primary focus on White European populations and reliance on opinion in areas lacking robust data (e.g., "false-positive" autoantibodies).
- Longitudinal monitoring of C-peptide may be valuable in cases with diagnostic uncertainty.
- Practical challenges exist in the clinical measurement and interpretation of C-peptide levels.

Key Knowledge Gaps

- Limited epidemiological data on adult-onset T1D prevalence, especially globally.
- Lack of diverse international registries.
- Uncertainty about the timing of autoimmunity onset and progression rates in adults.
- Poorly defined understanding of "biologic" false-positive autoantibodies.
- Need for more research on genetic risk differences across the age spectrum of T1D.
- Limited longitudinal data on metabolic changes (C-peptide, insulin resistance) in adults, particularly prior to seroconversion.
- Lack of validated diagnostic tools and biomarkers to distinguish adult-onset T1D from atypical T2D.
- Limited guidance on optimal screening, classification, and treatment strategies for adult-onset T1D.
- Unclear long-term impact of misclassification on outcomes and complications.
- Unknown age-related differences in exocrine pancreas loss.

Opportunities for Increased Understanding:

- Conducting large-scale epidemiological studies with diverse populations.
- Establishing comprehensive adult-onset T1D registries with detailed clinical, immunological, and genetic data.
- Performing longitudinal natural history studies, including periods before seroconversion.
- Refining and validating diagnostic algorithms and biomarkers for adult-onset T1D.
- Investigating the genetic and immunologic underpinnings of adult-onset disease.
- Characterizing the metabolic trajectories and the role of factors like obesity and insulin resistance.
- Evaluating the impact of different treatment approaches in adults, including disease-modifying therapies and adjuvant therapies.
- Standardizing C-peptide measurement and interpretation in clinical practice.
- Developing age-specific guidelines for diagnosis and management.

Conclusion:
Adult-onset T1D is a significant and often underrecognized form of diabetes with distinct characteristics compared to its childhood counterpart. The high rate of misdiagnosis underscores the urgent need for more research to address the existing knowledge gaps in its epidemiology, pathogenesis, diagnosis, and treatment. By focusing on these areas, the field can move towards earlier and more accurate identification of adult-onset T1D, ultimately improving patient outcomes and reducing the burden of this chronic disease.