**SUMMARY (basics) 7/7/25**

**ciT1zen science**

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The understanding of Type 1 Diabetes (T1D) has evolved significantly since the discovery of insulin transformed it from a fatal disease to a chronic condition. While insulin therapy has saved millions, T1D continues to be associated with considerable morbidity and mortality, underscoring the urgent need for disease-modifying therapies. The recent FDA approval of teplizumab, the first disease-modifying therapy to delay clinical T1D onset, marks a pivotal shift, treating T1D as an immunologic disease rather than solely a metabolic one. This briefing document synthesizes current knowledge, highlights critical gaps, and proposes future research endeavors to advance T1D understanding, prevention, and treatment. Key areas of focus include genetics, heterogeneity of the disease, pancreatic pathology, β-cell assessment, immunological biomarkers, the role of the exocrine pancreas, and population screening strategies. A central theme is the increasingly recognized heterogeneity of T1D and the need for precision medicine approaches.

Key Themes and Most Important Ideas/Facts

1. Evolution of T1D Understanding and Staging

The traditional view of T1D as a rapid, uniform onset has been refined. T1D is now understood to occur over months to years, a concept formalized by a **staging paradigm**:

* **Stage 0:** Pre-autoimmunity, little is known about immune cells and β-cells during this critical period.
* **Stage 1:** Presence of two or more β-cell-directed autoantibodies (e.g., GAD, insulin, IA-2, ZnT8) with normal glucose tolerance. These autoantibodies are "markers of T1D-related autoimmunity and predict, on a population level, subsequent development of dysglycemia."
* **Stage 2:** Multiple islet autoantibodies accompanied by dysglycemia, but not yet meeting diabetes diagnostic criteria.
* **Stage 3:** Hyperglycemia with β-cell-directed autoimmunity, meeting diabetes diagnostic criteria.

While a "progressive (and smoothly) declines" β-cell mass is often depicted from Stage 1 to 3, the exact "longitudinal changes and patterns of loss of β-cell mass shown in the schematic are mostly conjecture" due to measurement limitations in living humans. Some hypotheses suggest irregular decline or a "tipping point where β-cell mass and function rapidly decline 1 to 2 years prior to stage 3 T1D."

2. Genetic Contributions to T1D

Genetics play a clear role in T1D, with:

* **HLA Locus Dominance:** The "major driver of genetic risk for T1D resides in the HLA locus within the class II region (eg, HLA-DR, HLA-DQ)." Specific alleles like HLA-DQ8, DQ2, DR4, and DR3 confer significant risk, while "HLA-DQ6 ( *DQB1*06:02\* ) provides nearly dominant protection."
* **Polygenic Nature:** T1D is a polygenic disorder, with "more than 75 minor loci throughout the genome" contributing to risk, often influencing β-cells, immune cell function, or both.
* **Polygenic Risk Scores (GRS):** GRS, combining HLA and non-HLA loci, "may help identify individuals at-risk of developing T1D." However, "most individuals with high genetic risk not developing clinical T1D."
* **Knowledge Gaps:** Understanding genetic drivers of β-cell mass/loss, how specific genes (like *INS*) affect immune/β-cell function, and the epigenetics involved in islet autoimmunity.
* **Future Efforts:** Integrating whole-genome sequencing for early risk identification, refining GRS for diverse ancestries, and investigating functional genetics.

3. Heterogeneity of T1D

T1D is not a singular disease but exhibits "considerable heterogeneity on several levels." This variability impacts prognosis and treatment efficacy.

* **Clinical Variability:** "Age of onset, immunologic variability, and rates and degree of β-cell loss differ among individuals." T1D can manifest "over a broad age range in children, adolescents, and adults (<5 years to >70 years)."
* **Age-Specific Differences:** "Insulitis...in children having a greater absolute number of CD45+ immune cells...higher CD20+ B lymphocytes, and a more rapid loss of β-cells." Adult-onset T1D differs in genetic risk, hyperglycemia severity, immune response intensity, and β-cell loss rate.
* **Diagnostic Challenge:** Adult-onset T1D often leads to misclassification due to overlap with insulin resistance, highlighting the need to treat "both underlying mechanisms of diabetes development."
* **Implications for Clinical Trials:** Heterogeneity creates "challenges for assessing the efficacy of therapeutics," with a "strong rationale [existing] to dissect disease heterogeneity...to identify pathways that can be therapeutically targeted."
* **Knowledge Gaps:** Determining if childhood and adult-onset T1D have different pathogenic processes, understanding the natural history and pathology of adult-onset T1D, and whether defining heterogeneity improves treatment efficacy.
* **Future Efforts:** Establishing T1D "subtypes considering age, genetics, islet autoantibody profiles," actively seeking organ donors in early T1D stages for detailed study, and studying the natural history of adult-onset T1D.

4. Pancreatic Pathology in T1D

Understanding the specific changes in the human pancreas is crucial but challenging due to biopsy difficulties.

* **Key Discoveries (Autopsy Studies):** Modest "insulitis" (islet immune cell infiltration), "lobular loss of β-cells," and "hallmark hyperexpression of HLA class I within residual insulin-containing islets."
* **nPOD Contributions:** The Network for Pancreatic Organ Donors with Diabetes (nPOD) and Human Pancreas Analysis Program (HPAP) have significantly advanced understanding of "human islet architecture, islet composition, and immune infiltration."
* **Beyond Autoimmunity:** "Other mechanisms of β-cell loss or dysfunction...may contribute to T1D," including dedifferentiation, transdifferentiation, and stress-induced senescence.
* **Scarcity of Samples:** "Few individuals die at the onset of T1D or in the autoimmunity phase," limiting tissue availability at critical timepoints.
* **Knowledge Gaps:** Baseline β-cell mass in at-risk individuals, earliest islet lesions (and their consistency across individuals/ethnicities), longitudinal patterns of β-cell loss, and reasons for β-cell survival/regeneration.
* **Future Efforts:** Greater efforts to procure pancreata from at-risk and recent-onset donors, expanding bioresources from diverse ethnicities, and improving understanding of normal pancreatic development.

5. Assessment of β-cell Function and Mass

Indirect assessment of β-cell function is done by measuring insulin and C-peptide:

* **C-peptide as Gold Standard:** "C-peptide is secreted in a 1:1 molar ratio from β-cells" and is the "gold standard for assessment of β-cell function and secretory capacity."
* **Progression of β-cell Dysfunction:** Loss of first-phase insulin secretion and C-peptide impairments detected "as early as 6 years prior to diagnosis" in children. "Rapid metabolic deterioration begins 1 year to 6 months prior to stage 3 T1D onset."
* **β-cell Mass Measurement Challenges:** "It is currently not possible to measure β-cell mass in living humans." Provocative tests provide some insight, but "β-cell function and mass do not correlate in different T1D stages," possibly implying that "a portion of β-cells may be 'sleeping' or recoverable."
* **Knowledge Gaps:** C-peptide changes *before* autoantibody development, modification of C-peptide decline by genetic/other factors, and noninvasive β-cell mass quantification methods.
* **Future Efforts:** Developing and validating methods to monitor β-cell function and mass simultaneously, leveraging metabolic progression knowledge for optimal therapy timing, and continuing development of clinical β-cell tracers for *in vivo* imaging.

6. Immunological Biomarkers

Beyond autoantibodies, the search for reliable biomarkers reflecting the autoimmune process is ongoing:

* **Autoantibodies as Predictors:** "The presence of 2 or more autoantibodies...make T1D a predictable disease as their number and levels predict, on a population level, time to progression to stage 3 T1D." However, they "do not reliably predict progression and timing of clinical T1D onset" at the individual level.
* **Challenges in Soluble/Cellular Biomarkers:** Despite extensive research, "inconsistent reproduction of these results across different studies" for serum metabolites, proteins, nucleic acids, and immune cell subsets.
* **Combinatorial Profiles:** "Combinatorial biomarker profiles may eventually be leveraged to dissect disease heterogeneity to allow for better classification of T1D subtypes."
* **T-cell Receptor Sequencing:** A promising area is sequencing T-cell receptors (TCRs) to identify "pancreatic islet-derived T-cell receptor sequences from peripheral blood DNA or RNA." "Remarkably, a number of these pancreatic islet-derived T-cell receptor sequences are shared among patients, and these cells circulate in the peripheral blood."
* **Knowledge Gaps:** Evolution of immune cell subsets across T1D stages in different tissues, primary antigens involved in T1D initiation, and properties distinguishing antigen-specific T cells in T1D from healthy individuals.
* **Future Efforts:** Expanded use of high-dimensional imaging and single-cell technologies, validating blood-based biomarkers of disease activity, leveraging longitudinal studies, and standardizing assays.

7. Role of the Exocrine Pancreas

T1D research has expanded to include the exocrine pancreas:

* **Reduced Pancreas Size:** Studies show "a reduction in total pancreas size and the presence of inflammatory infiltrates in pancreatic exocrine tissue." This reduction is seen early after diagnosis and even in autoantibody-positive individuals in Stage 1 or 2, and "autoantibody-negative first-degree relatives of individuals with T1D also appear to have a slightly smaller pancreas volume."
* **Insulin Deficiency Impact:** "Insulin deficiency, even in the absence of islet-directed autoimmunity, is sufficient to reduce exocrine pancreas size," as observed in monogenic diabetes forms.
* **Histological Changes:** Long-standing T1D pancreata show "fewer acinar cells and increased fibrosis," and "greater number of CD45+, CD4+, and CD8+ T cells in the exocrine tissue."
* **Knowledge Gaps:** Whether exocrine changes are primary or secondary, the cause of reduced pancreas mass, and its relationship to β-cell mass/function.
* **Future Efforts:** Investigating determinants of pancreas mass (genetic, environmental), standardized longitudinal pancreatic imaging, and linking pancreatic tissue studies with single-cell analysis and clinical information.

8. Screening and Intervention Strategies

Shifting from family history-based screening to general population screening:

* **Need for Population Screening:** "Up to 90% of people who develop T1D do not have a family member with T1D."
* **Feasibility Demonstrated:** Studies like Fr1da (Bavaria), Autoimmunity Screening for Kids (US), and T1Early (UK) support the feasibility of "broad population-based screening for T1D-associated autoantibodies."
* **Benefits of Screening:** Decreased likelihood of life-threatening diabetic ketoacidosis and identification of individuals for disease-modifying therapy (e.g., teplizumab) to delay clinical onset.
* **Role of Genetic Screening:** "Genetic screening at birth for HLA haplotype or polygenic risk scores for T1D could identify individuals with an increased likelihood of developing islet autoantibodies," narrowing the population for longitudinal autoantibody screening.
* **Diversity in GRS:** Recognition of the need for "distinct African American T1D GRS" to address poor performance of European ancestry GRS in diverse populations.
* **Knowledge Gaps:** Transitioning screening from research to clinical practice, optimal screening approach (genetic vs. autoantibody-first), identifying at-risk adults, and effective communication of risk.
* **Future Efforts:** Monitoring outcomes of ongoing screening studies for feasibility and acceptability, considering randomized controlled trials for screening approaches, and developing T1D registries.

9. Future Directions and Unresolved Questions

A comprehensive understanding of T1D requires interdisciplinary efforts and addresses several overarching questions:

* **Bidirectional Pathogenesis:** T1D pathogenesis is likely a "bidirectional process in which both the immune system and the pancreas/islet are active participants."
* **Molecular-Clinical Connection:** How to link "advances in molecular understanding" with "new clinical approaches" and vice-versa.
* **Defining Islet/Immune Interaction:** Better defining islet cell composition, architecture, microenvironment, and immune cell repertoire, and their interactions.
* **Translational Biomarkers:** Can 'omics technologies (transcriptomics, proteomics, lipidomics, metabolomics) identify new biomarkers for clinical trials?
* **Data Diversity:** Ensuring data collection is not skewed by ethnicity, age, or disease duration.
* **Control Samples:** Ensuring access to appropriate age-matched healthy control samples.
* **Integration of Data:** Integrating information from isolated islets/pancreatic tissue studies with clinical studies in at-risk individuals.
* **Interdisciplinary Teams:** Recognizing and encouraging interdisciplinary collaborations.

"More than 100 years after the discovery of insulin, the field is poised to again make rapid progress in the understanding, prevention, and treatment of T1D." Access to human tissue, novel technologies, and new disease-modifying therapies offer the potential to "greatly improve the quality of life for those impacted by T1D."

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