SUMMARY (Clinical) 6/20/25 ciT1zen science

Type 1 Diabetes Prevention: Present and Future Horizons ciT1zen science summary

Source: Nature Reviews, June 17, 2025, Forbes etal Type 1 diabetes mellitus prevention: present and future. https://www.nature.com/articles/s41574-025-01128-6

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease with increasing global incidence that necessitates lifelong exogenous insulin therapy and carries a significant risk of complications and mortality. Historically viewed as solely a T cell-mediated disease, recent understanding highlights the active role of β-cells in immune-mediated damage, emphasizing their heterogeneity, vulnerability to stressors, and ability to act as antigen-presenting cells. While an effective cure remains elusive, significant research efforts are focused on developing therapeutic strategies to prevent or delay T1DM onset.
Currently, teplizumab is the only FDA-approved therapy for delaying T1DM onset in high-risk individuals. However, its intravenous administration, generalized immunosuppression, and adverse effects present challenges for routine clinical practice. Emerging research points towards alternative approaches, such as targeting the Receptor for Advanced Glycation End Products (RAGE), a pro-inflammatory molecule upregulated in T1DM on β-cells and immune cells. This briefing details the current understanding of T1DM pathogenesis, existing prevention strategies, and promising future therapeutic avenues.

Key Themes and Facts

1. The Evolving Understanding of T1DM Pathogenesis

- **Autoimmune Nature:** T1DM is an autoimmune disease characterized by the immune system's destruction of insulin-producing β-cells in the pancreas, leading to insulin deficiency. This process often involves the presence of islet autoantibodies.
- **Beyond T-cell Centricity:** While T1DM was "historically... solely described as a T cell-mediated disease," current understanding acknowledges "the role of β-cells as active participants in the immune-mediated damage." This shift in perspective is crucial for developing effective prevention strategies.
- **β-Cell Vulnerability and Role:** β-cells exhibit "heterogeneity, vulnerability to stressors and the ability... to act as antigen-presenting cells," which fundamentally alters the approach to disease prevention and β-cell preservation.
- **Stages of T1DM Development:** The disease progresses through distinct stages:
- **Stage 1 (Pre-symptomatic):** Characterized by the presence of two or more islet autoantibodies and normal glucose metabolism.
- **Stage 2 (Pre-symptomatic):** Involves two or more islet autoantibodies and dysglycemia (abnormal glucose levels) but without clinical symptoms.
- **Stage 3 (Clinical Diagnosis):** Marked by symptomatic hyperglycemia.
- **Genetic and Environmental Factors:Genetics:** Genetic predisposition, particularly in the HLA region, plays a significant role.

- **Environmental Triggers:** Viruses (e.g., enteroviruses), diet, and other environmental factors are implicated. For instance, "excess consumption of ultraprocessed foods" is linked to the accumulation of Advanced Glycation End Products (AGEs).

2. Current Prevention Strategies and Their Limitations

- **Teplizumab: The Only FDA-Approved Therapy:** "Teplizumab, an Fc-receptor non-binding humanized CD3-specific monoclonal antibody, is the only therapy approved by the FDA for the delay of T1DM onset."
- **Mechanism:** Teplizumab targets CD3, a molecule on T cells, aiming to modulate the immune response and preserve β-cell function. It has been shown to "preserve C-peptide in recent-onset type 1 diabetes."
- **Challenges:** Its "intravenous administration, generalized immunosuppression and adverse effects mean that the transition to routine clinical practice is not without challenges." Common adverse effects include lymphopenia and rash.
- **Impact:** Despite challenges, teplizumab's approval is a significant step, potentially "leading to the development of more accessible therapies."
- **Historical and Investigational Therapies:Generalized Immunosuppression (e.g., Cyclosporine):** Early attempts showed promise in preserving β-cell function but were limited by "nephrotoxicity and other adverse effects."
- **Antigen-Specific Immunotherapies:Oral/Nasal Insulin:** Aimed at inducing immune tolerance but "failed to prevent T1DM."
- **Intralymphatic GAD-alum:** Shows some promise in preserving β-cell function, particularly in patients with specific HLA genotypes.
- **Broad Immunomodulatory Agents:Anti-thymocyte globulin (ATG):** Demonstrated efficacy in preserving β-cell function but with associated adverse effects.
- **Abatacept (CTLA4-Ig):** A costimulation modulator that has shown some benefit in delaying progression to clinical diabetes in at-risk individuals.
- **Low-dose Interleukin-2 (IL-2):** Explored for its potential to expand regulatory T cells.
- **Ustekinumab (Anti-IL-12/23):** Currently in clinical trials for adolescents, showing some positive effects on C-peptide preservation.
- **Rituximab (Anti-CD20):** B-lymphocyte depletion has been explored, showing some preservation of C-peptide.
- **Baricitinib (JAK1/2 inhibitor):** A promising oral therapy that has shown positive effects on β-cell function, potentially by blocking interferon-α signaling.
- **Verapamil (Calcium channel blocker):** Repurposed drug showing potential in improving β-cell function, particularly in newly diagnosed pediatric patients.

3. Future Directions: Targeting RAGE and Beyond

- **Receptor for Advanced Glycation End Products (RAGE):** A key focus for future prevention strategies.
- **Role in T1DM:** RAGE is a "pro-inflammatory molecule involved in host–pathogen defence and is upregulated during T1DM on β-cells and immune cells (including T cells)." It is activated by various ligands, notably Advanced Glycation End Products (AGEs).
- **AGEs:** "Advanced glycation end products (AGEs), such as HbA1c, are formed in the body and accumulate with age, metabolic abnormalities (including diabetes mellitus) and via excess consumption of ultraprocessed foods." They contribute to β-cell dysfunction and inflammation.

- **Therapeutic Potential:** "Targeting the receptor for advanced glycation end products (RAGE)" offers an "alternative approach" to decrease inflammation and potentially preserve β-cells.
- **RAGE Antagonists (e.g., Azeliragon):** While primarily investigated for Alzheimer's disease, RAGE antagonists have potential for T1DM by inhibiting inflammatory pathways.
- **Soluble RAGE (sRAGE):** Circulating sRAGE can act as a "decoy receptor" for AGEs, preventing their interaction with cell-surface RAGE. Lower sRAGE levels are associated with increased risk of T1DM development.
- **Combined Therapies:** Given the complex multifactorial nature of T1DM, future approaches are likely to involve combination therapies targeting different aspects of the disease.
- **Early Intervention:** Identifying individuals at high risk (e.g., through screening for autoantibodies) before symptomatic onset is crucial, as intervention during earlier stages can "result in milder diabetes at clinical manifestation" and potentially prevent complications like diabetic ketoacidosis (DKA) at diagnosis.

Conclusion

The landscape of T1DM prevention is evolving from a T-cell-centric view to one that recognizes the active role and vulnerability of β-cells. While teplizumab offers a crucial first step in delaying disease onset, its limitations highlight the need for more accessible and targeted therapies. The investigation into RAGE and AGEs presents a promising new avenue, linking environmental factors like diet to the inflammatory processes in T1DM. Continued research into novel immunotherapies and combination strategies, alongside early identification of at-risk individuals, holds the key to ultimately preventing or significantly altering the course of Type 1 Diabetes Mellitus.