SUMMARY (Clinical) 5/30/25 ciT1zen science

Partial remission of type 1 diabetes: Do immunometabolic events define the honeymoon period? ciT1zen science summary

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Overview: This review article explores the phenomenon of partial clinical remission, often called the "honeymoon phase," in Type 1 Diabetes (T1D). It posits that this transient period of improved glucose control, characterized by residual endogenous insulin production and reduced exogenous insulin requirements, is significantly influenced by the interplay of immunometabolic events. The authors propose that maintaining better glucose control can delay the detrimental effects of autoimmune mechanisms in pancreatic islets, thereby extending this remission phase. The review highlights how glucose metabolism impacts immune cell activity (macrophages and T-cells) and β-cell function, suggesting that targeting these pathways offers novel opportunities for therapeutic intervention.
Key Themes and Ideas:

- **Partial Clinical Remission ("Honeymoon Phase"):** This is a transient phase in T1D following diagnosis where there is improved glucose control due to continued endogenous insulin production by residual β-cells. It is heterogeneous in duration (months to years) and its definition varies, although parameters like HbA1C, insulin usage, and the insulin dose-adjusted A1C (IDAA1C) are used.
- **Quote:** "Partial clinical remission in Type 1 diabetes (T1D) refers to a transient phase of improved glucose control following diagnosis. During this period, endogenous islet β-cells continue to produce and secrete insulin, resulting in lower exogenous insulin requirements and improved glycaemic status."
- **Quote:** "Partial remission is often described colloquially as the ‘honeymoon phase’, a period lasting from months to years which is heterogeneous across patient groups."
- **Heterogeneity of Remission:** The likelihood and duration of the honeymoon phase are not uniform across individuals. Factors influencing this include age of onset (adults more likely than children), presence of GAD autoantibodies (associated with greater insulin requirements), and glycemic control during follow-up. Obesity and insulin resistance may hinder partial remission.
- **Immunometabolic Events as Drivers of Remission Duration:** The central hypothesis is that the duration of partial remission is controlled by the interplay between glucose metabolism and immune cell-driven inflammatory and autoimmune processes.
- **Quote:** "We thus propose that precise control of blood glucose within a healthy range delays the deleterious consequences that arise from autoimmune mechanisms within pancreatic islets, ultimately leading to the extension of the honeymoon phase."

- **Restoring Normoglycemia Improves Residual β-Cell Function:** Lowering blood glucose is proposed to trigger partial remission by:

1. Restoring glucose-stimulated insulin secretion in residual β-cells.
2. Reducing pathogenic responses of autoreactive immune cells.

- **Quote:** "Therefore, we propose that lowering blood glucose may trigger partial remission through two main strategies: restoring glucose-stimulated insulin secretion in residual β-cells (if only temporarily) and reducing pathogenic responses of autoreactive immune cells..."
- **Hyperglycemia Impairs β-Cell Function:** Prolonged exposure to high glucose levels negatively impacts β-cell function, leading to reduced insulin secretion, loss of maturity markers, and alterations in gene expression.
- **Quote:** "Prolonged exposure of β-cells to hyperglycaemic conditions impairs the ability of β-cells to secrete insulin in response to a subsequent glucose challenge."
- **Quote:** "Moreover, as mentioned above, hyperglycaemic conditions promote dedifferentiation and/or loss of maturity markers in β-cells."
- **Glucose Metabolism and Reduced β-Cell Function:** The authors suggest increased flux through the hexosamine biosynthesis pathway (HBP) in β-cells due to excess glucose as a possible mechanism for reduced insulin secretion.
- **Cytokine Signaling and β-Cell Dysfunction:** Islet β-cells are exposed to pro-inflammatory cytokines (e.g., IL-1β, IFNγ) secreted by immune cells. Chronic exposure to these cytokines, similar to hyperglycemia, suppresses glucose-stimulated insulin secretion and promotes loss of β-cell maturity markers.
- **Quote:** "Thus, both chronic hyperglycaemia and prolonged exposure to pro-inflammatory cytokines are likely to be key events suppressing glucose-stimulated insulin secretion in the context of T1D."
- **Macrophage Production of IL-1β is Coupled to Glucose Metabolism:** Hyperglycemia provides an excess substrate pool that can sustain IL-1β synthesis and secretion from macrophages, contributing to inflammation within the islets.
- **Quote:** "While speculative, it is conceivable that hyperglycaemia provides an excess substrate pool by which to sustain IL-1β synthesis and secretion from macrophages during T1D..."
- **Quote:** "Based on existing data, enhanced glucose metabolism supports macrophage function, which could reveal how hyperglycaemia prior to autoantibody production may drive T1D disease onset and progression."
- **IFNγ Production in Effector T-Cells is Linked to Glucose Metabolism:** Activated T-cells require glucose metabolism to support their proliferation and cytokine production, particularly IFNγ. Glycolysis selectively facilitates the translation of IFNγ mRNA into protein.
- **Quote:** "Thus, metabolism through glycolysis selectively facilitates the translation of IFN-γ mRNA into IFN-γ protein in activated T-cells, thereby linking glucose metabolism as a regulatory signal for progression and maintenance of effector function."
- **Quote:** "We postulate that these observations have major implications for maintaining careful glucose control in T1D to limit activated T-cell function and thus potentially induce or extend a partial remission period..."

- **Therapeutic Implications:** Understanding these immunometabolic connections offers opportunities for intervention. Restoring glycemic control (e.g., with insulin) is predicted to reduce pathological outcomes. Immunomodulatory strategies (e.g., baricitinib, teplizumab) that limit autoimmune responses can also extend the honeymoon phase.
- **Quote:** "Consequently, restoring blood glucose levels to a physiological range, such as with insulin therapy, is predicted to reduce the pathological outcomes driving autoimmunity and restore the ability of residual islet β-cells to respond to stimuli."
- **Quote:** "This partial remission phase can be extended in discrete populations with interventions that further reduce autoimmune responses targeting islet β-cells (e.g. baricitinib or teplizumab)."
- **Preserving Residual β-Cell Function:** The authors emphasize the consensus that preserving endogenous β-cell function is beneficial for patients, reducing the risk of complications.
- **Quote:** "There is a consensus that preserving endogenous β-cell function for as long as possible benefits the patient by reducing the risk of hypoglycaemia and vascular complications."
- **Future Directions:** A deeper understanding of the impact of glycemia on different islet and immune cell types is needed to develop precision medicine approaches for T1D, with the ultimate goal of permanent β-cell recovery.

Most Important Ideas/Facts:

- Partial remission in T1D is a significant but heterogeneous phase influenced by immunometabolic events.
- Hyperglycemia has detrimental effects on both β-cell function and the activity of key immune cells (macrophages and T-cells) involved in autoimmunity.
- Glucose metabolism directly fuels the production of pro-inflammatory cytokines like IL-1β (by macrophages) and IFNγ (by effector T-cells).
- Restoring and maintaining good glycemic control, along with immunomodulatory therapies, can help extend the partial remission period by mitigating these detrimental immunometabolic effects.
- Preserving residual β-cell function during the honeymoon phase is crucial for improving patient outcomes.