**SUMMARY (Clinical) 7/7/25**

**ciT1zen science**

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Source: Persisting plasma proinsulin levels in a cohort of 482 individuals with long-standing type 1 diabetes mellitus

Main Theme: Proinsulin as a Potential Marker for Stressed, Yet Viable Beta-Cells in Type 1 Diabetes Mellitus

This study investigates the behavior of plasma proinsulin levels in individuals with long-standing Type 1 Diabetes Mellitus (T1D), particularly in comparison to C-peptide levels. The central hypothesis is that detectable proinsulin, even in the absence of C-peptide, could signify the presence of "stressed, yet alive β-cells." This is significant because current immune-modifying interventions in T1D aim to preserve beta-cell viability, but lack reliable biomarkers for this specific purpose.

Most Important Ideas/Facts:

1. **Biphasic Decline of Proinsulin and C-peptide:**

* **Proinsulin:** Shows a biphasic decline over time after T1D diagnosis, with an initial decrease over approximately 15 years, followed by a "stabilisation period."
* **C-peptide:** Exhibits a similar biphasic decline, but with an earlier "inflection point at ≈8 years."
* **Quote:** "Proinsulin showed a biphasic decline with an initial decrease over 15 years followed by a stabilisation period, whereas C-peptide showed a similar pattern but with an inflection point at 8 years."

1. **Proinsulin Detectability in the Absence of C-peptide:**

* A remarkable finding is that "59% of the individuals without fasted C-peptide secretion had detectable proinsulin levels." This directly supports the hypothesis that proinsulin can be a marker for beta-cells that are still alive but may be dysfunctional in their ability to process proinsulin into insulin and C-peptide.
* **Quote:** "In type 1 diabetes mellitus, proinsulin levels remain detectable long after diagnosis, also in the absence of C-peptide, implying the presence of stressed, yet alive β-cells."

1. **Proinsulin-to-C-peptide Ratio (PI:C) as a Marker of Beta-Cell Stress:**

* An elevated PI:C ratio is frequently associated with β-cell stress and inadequate processing of proinsulin.
* The study found that "the PI:C increases in the first 10–20 years after diagnosis, followed by stabilization at levels similar to the first year of diagnosis," suggesting that even when C-peptide is undetectable, proinsulin can still be released but not properly cleaved.
* **Quote:** "Elevated proinsulin levels, expressed as an elevated proinsulin-to-C-peptide ratio (PI:C), are frequently associated with β-cell stress, can precede the onset of type 1 diabetes mellitus and mark dyseyseisease progression due to inadequate processing of proinsulin or insulin resistance."
* However, the study "could not relate PI:C to parameters of inflammation (leukocytes, CRP) or insulin resistance (BMI, triglycerides, insulin use/kg)."

1. **Correlation with Autoantibodies and HLA Haplotypes:**

* **Anti-GAD Antibodies:** Higher proinsulin and C-peptide levels correlated with higher levels of anti-GAD antibodies. This supports the notion that "anti-GAD antibodies are associated with a slower course of type 1 diabetes mellitus with preservation of residual beta cells."
* **Anti-IA2 Antibodies:** No correlation was found between proinsulin/C-peptide and anti-IA2 antibodies.
* **HLA Genotype:** A "high-risk DR3/3 HLA genotype associated with complete loss of C-peptide (OR 0.34, 95% CI 0.14–0.79) and proinsulin (OR 0.44, 95% CI 0.20–0.92)." This implies that HLA haplotypes, particularly high-risk ones, play a role in the extent of beta-cell destruction, impacting both proinsulin and C-peptide secretion.

1. **Implications for Beta-Cell Preservation Strategies:**

* The persistence of proinsulin, independently of C-peptide, makes it a valuable candidate biomarker for beta-cell viability. This is especially relevant for "immune modifying interventions [that] primarily aim to preserve β-cell viability rather than β-cell function," as these trials currently "lack an established biomarker to quantify this."
* **Quote:** "Since in longstanding type 1 diabetes mellitus proinsulin is detectable independently of C-peptide, proinsulin may serve as a marker of surviving but dysfunctional β-cells in type 1 diabetes mellitus."
* **Quote:** "Our observations warrant confirmation in mechanistic studies to establish whether proinsulin can serve as a surrogate measure of β-cell mass, akin to C-peptide as a surrogate for β-cell function."

Study Design and Population:

* **Cohort:** Cross-sectional cohort of 482 individuals with long-standing T1D from the GUTDM1 study.
* **Measurements:** Fasting proinsulin, C-peptide, anti-GAD, anti-IA2 autoantibodies, and HLA genotypes were measured.
* **Participant Characteristics:** 63% females, median age 41 years, median diabetes duration 16 years.
* **Detectability:** Plasma proinsulin levels were detectable in 69% of the total population, while plasma C-peptide levels were detectable in 31%.

Limitations:

* **Cross-sectional Design:** The study uses cross-sectional data, meaning conclusions about decline over time are based on diabetes duration as an estimate, rather than direct longitudinal observation.
* **Assay Sensitivity Differences:** Differences in the detection limits for proinsulin (<0.15 pmol/L) and C-peptide (<0.05 nmol/L) might underestimate the proportion of secretors. However, the distinct stabilization patterns and PI:C increase suggest the observed differences are not solely due to assay sensitivity.
* **Adult-Only Cohort and Limited Short/Very Long Duration Cases:** The study primarily includes adults and has limited data for individuals with very short or very long diabetes durations, which could affect the generalizability of decline estimates.

Conclusion:

The study provides novel insights into the dynamics of proinsulin secretion in long-standing T1D, highlighting its potential as a distinct marker for surviving, albeit stressed or dysfunctional, beta-cells. This finding is crucial for the development and assessment of future T1D therapies aimed at preserving beta-cell mass, suggesting that proinsulin could become a valuable surrogate measure alongside C-peptide.

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