SUMMARY (Clinical) 5/2/25 ciT1zen science

Repeated OGTT Versus Continuous Glucose Monitoring for Predicting Development of Stage 3 Type 1 Diabetes: A Longitudinal Analysis
ciT1zen science summary

Source: Repeated OGTT Versus Continuous Glucose Monitoring for Predicting Development of Stage 3 Type 1 Diabetes: A Longitudinal Analysis (Desouter et al., Diabetes Care 2025;48(4):528–536)
Date: Feb 4 2025
Subject: Review of findings regarding the diagnostic performance of repeated Oral Glucose Tolerance Tests (OGTTs), Continuous Glucose Monitoring (CGM), and HbA1c for predicting progression to Stage 3 Type 1 Diabetes (T1D) in multiple autoantibody-positive first-degree relatives.
Key Takeaways:

- **Longitudinal Comparison:** This study provides longitudinal data comparing the predictive performance of repeated OGTTs, CGM, and HbA1c in identifying multiple autoantibody-positive first-degree relatives (FDRs) who will progress to Stage 3 T1D. This is a significant contribution as previous evidence for CGM in presymptomatic T1D was primarily cross-sectional.
- **Repeated OGTTs Remain Superior in Longitudinal Models:** While repeated CGM metrics and HbA1c were found to be nearly as effective as repeated OGTTs in predicting stage 3 T1D in longitudinal analysis, OGTTs, particularly OGTT-derived AUC glucose and C-peptide/glucose ratio, consistently outperformed CGM and HbA1c in terms of model fit (lower AICc values).
- **CGM and HbA1c's Role in Monitoring:** Despite being outperformed by OGTTs in longitudinal predictive models, the study suggests that repeated CGM and HbA1c may be more practical and convenient for long-term clinical monitoring, especially in young children, due to the invasiveness and time commitment associated with OGTTs.
- **Variability Observed:** Both OGTT and CGM metrics showed considerable intra- and interindividual variability over time, highlighting the dynamic nature of glucose dysregulation in the presymptomatic phase.
- **Cross-Sectional Performance:** In baseline (cross-sectional) analysis, the best performing OGTT and CGM metrics showed similar predictive performance for rapid progression to stage 3 T1D. CGM metrics like time $\ge$140 mg/dL and $\ge$120 mg/dL and OGTT-derived AUC glucose were strong predictors in this context.
- **Clinical Implications:** OGTTs remain important for disease staging and as entry/outcome criteria in clinical trials and for disease-modifying therapies like teplizumab. However, for routine, long-term monitoring, especially in younger individuals, CGM and HbA1c offer a less burdensome alternative. Aberrant results from CGM or HbA1c should be confirmed, potentially with an OGTT.

Research Question and Methods:
The study aimed to evaluate the diagnostic performance of serial CGM, HbA1c, and OGTT metrics to predict progression to stage 3 type 1 diabetes based on longitudinal data from 34 multiple autoantibody-positive first-degree relatives (FDRs). Participants were monitored semiannually with 5-day CGM recordings, HbA1c, and OGTTs for a median of 3.5 years. Longitudinal patterns were analyzed, and prediction of rapid (<3 years) and overall progression to stage 3 T1D was assessed using various statistical methods including ROC analysis, Kaplan-Meier method, and Cox proportional hazards models (baseline and extended with time-varying covariates).
Key Findings and Supporting Evidence:

- **Progression to Stage 3:** After a median follow-up of 40 months, 17 of the 34 FDRs developed stage 3 T1D.
- **Longitudinal Trends:**"Semiannual CGM metrics, especially when complemented by HbA1c, can predict stage 3 development but are outperformed by repeated OGTTs."
- Longitudinal spaghetti plots (Figure 2) illustrated that OGTT-derived stimulated glucose metrics, HbA1c, and CGM-derived time $\ge$120 mg/dL and $\ge$140 mg/dL generally increased in progressors in the years leading up to diagnosis, mirroring changes in OGTTs.
- This rise was accompanied by a decrease in AUC C-peptide and AUC C-peptide/glucose ratio in progressors.
- Both OGTT and CGM metrics displayed "substantial intra- and interindividual variability."
- **Predictive Performance (Baseline Analysis - Rapid Progression <3 Years):**Significant ROC AUCs for rapid progression ranged between 0.75 and 0.86 for OGTT metrics and 0.77 and 0.92 for CGM metrics.
- "The best predictors for rapid progression were OGTT-derived AUC glucose and CGM-derived mean glucose, time $\ge$140 mg/dL (7.8 mmol/L), and time $\ge$120 mg/dL (6.7 mmol/L), reaching ROC AUCs >0.85."
- HbA1c alone was not a significant predictor in baseline analysis.
- Combining two CGM metrics did not improve the ROC AUC beyond the best individual CGM metric.
- **Predictive Performance (Baseline Analysis - Overall Progression):**Kaplan-Meier survival analyses effectively distinguished faster from slower progressors based on baseline metabolic assessments and ROC-derived cutoff values.
- Univariable Cox PH models confirmed OGTT-derived AUC glucose (concordance = 0.78) and glucose at T120 (concordance = 0.73) as strong predictors.
- CGM-derived time $\ge$120 mg/dL (concordance = 0.73) and time $\ge$140 mg/dL (concordance = 0.74) performed similarly to stimulated OGTT-derived variables.
- **Predictive Performance (Longitudinal Analysis):**In extended Cox PH models with time-varying covariates (n = 197 OGTTs with concomitant CGM recordings):
- HbA1c emerged as a significant individual predictor (AICc = 80.4).
- OGTT-derived AUC glucose (AICc = 71.1) outperformed CGM-derived time $\ge$120 mg/dL (AICc = 75.1) and HbA1c (AICc = 80.4).
- The best multivariable OGTT model (including glucose at T120 and AUC C-peptide, and HbA1c, or AUC glucose, AUC C-peptide, and HbA1c) remained superior (AICc = 62.7 and 58.9 respectively) to the best multivariable CGM model (combining mean glucose and IQR, AICc = 72.5).
- Combining CGM metrics with HbA1c improved the AICc (AICc = 68.4) compared to CGM alone, but was still outperformed by the best OGTT models.
- "In longitudinal models, repeated CGM and HbA1c were nearly as effective as OGTT in predicting stage 3 type 1 diabetes and may be more convenient for long-term clinical monitoring."

Discussion and Implications:

The study confirms the value of both OGTT and CGM in identifying individuals at risk of progressing to stage 3 T1D. While OGTTs demonstrate stronger predictive power in longitudinal models, the practical benefits of CGM and HbA1c, particularly for continuous and home-based monitoring, make them valuable tools in the clinical management of individuals at risk. The observed variability in glycemic metrics emphasizes the need for repeated testing and potentially a combination of methods for comprehensive assessment. The findings support existing recommendations for metabolic monitoring in autoantibody-positive individuals and provide evidence for the utility of CGM as a less invasive alternative or adjunct to OGTTs in specific scenarios.

Further Research Needs:

The authors highlight the need for further validation of these findings in more diverse populations, utilizing newer CGM technologies, and potentially with increased CGM frequency. Direct comparisons of the psychological impact, user acceptance, practical implementation, and cost-effectiveness of OGTT and CGM are

also warranted. Research is also needed to better predict stage 2 T1D and determine the optimal timing for confirmatory tests when considering interventions.